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Doctoral Program in Biomedical Engineering

PhD Thesis

**Development of nonlinear techniques based on
time-frequency representation and information
theory for the analysis of EEG signals to assess
different states of consciousness**

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Resumen

El registro de la señal Electroencefalográfica (EEG) proporciona información sobre los cambios en la actividad cerebral asociados con varios estados de la anestesia, la epilepsia, la atención cerebral, los trastornos del sueño, los trastornos cerebrales, etc. Los EEG son señales complejas cuyas propiedades estadísticas dependen del espacio y del tiempo. Sus características aleatorias y no estacionarias hacen imposible que el EEG se describa de forma precisa con una técnica sencilla requiriendo un análisis y una caracterización que implica técnicas que tengan en cuenta su no estacionariedad. Todo esto aumenta la necesidad de desarrollar nuevas técnicas avanzadas con el fin de mejorar la eficiencia de los métodos utilizados en la práctica clínica que son basados en el análisis de EEG.

En esta tesis se han investigado y aplicado diferentes métodos utilizando técnicas no lineales con el fin de desarrollar índices capaces de caracterizar el espectro de frecuencias, la dinámica no lineal y la complejidad de las señales EEG registradas en diferentes estados de conciencia. En primer lugar, se ha desarrollado un nuevo algoritmo basado en la envolvente de la señal para la eliminación de ruido de picos en las señales biológicas. Este algoritmo ha sido aplicado a señales simuladas y reales obteniendo resultados significativamente mejores comparados con los filtros adaptativos tradicionales. Seguidamente, se han llevado a cabo varios estudios con el fin de extraer y evaluar las medidas de EEG basadas en técnicas no lineales en diferentes contextos. Se han definido nuevos índices mediante el cálculo de la entropía de la distribución de Choi-Williams (DCW) con respecto al tiempo o la frecuencia. Se ha observado que los valores de estos índices tienden a disminuir, en diferentes proporciones, cuando el comportamiento de las señales evoluciona de caótico o aleatorio a periódico. Además, se han encontrado valores diferentes de estos índices aplicados a la señal EEG registrada en diferentes estados.

Diferentes medidas basadas en la representación tiempo-frecuencia, la función de información mutua y la correntropía se han aplicado al EEG para la detección automática de la somnolencia en pacientes que sufren trastornos del sueño. Se ha observado en la zona frontal que la potencia en la banda θ es mayor en los pacientes con somnolencia diurna excesiva, mientras que la entropía espectral y la entropía espectral cruzada en la banda δ es mayor en los pacientes sin somnolencia. En el grupo sin somnolencia se ha encontrado más complejidad en la zona occipital, mientras que el acoplamiento no lineal entre las regiones occipital y frontal ha resultado más fuerte en pacientes con somnolencia diurna excesiva, en la banda β .

La representación tiempo-frecuencia y las medidas no lineales se han utilizado para estudiar cómo la adaptación y la fatiga afectan a los potenciales cerebrales relacionados con estímulos térmicos, eléctricos y auditivos. Analizando el promedio de varias épocas de EEG grabadas después de la estimulación, se han encontrado diferencias entre las respuestas a la estimulación frecuente e infrecuente en diferentes períodos de registro.

Todas las técnicas que se han desarrollado, se han aplicado a señales EEG registradas en pacientes sedados, con el fin de predecir las respuestas a la estimulación del dolor. Un conjunto de medidas calculadas en señales EEG filtradas en diferentes bandas de frecuencia ha permitido mejorar la evaluación del nivel de sedación. Las

medidas propuestas han presentado un mejor rendimiento comparado con el índice bispectral, un indicador de hipnosis tradicional.

En conclusión, las medidas no lineales basadas en la representación tiempo-frecuencia, funciones de información mutua y correntropía han proporcionado informaciones adicionales que contribuyeron a mejorar la detección automática de la somnolencia, la caracterización y predicción de las respuestas nociceptivas y por lo tanto la evaluación del nivel de sedación.

Abstract

Electroencephalogram (EEG) recordings provide insight into the changes in brain activity associated with various states of anesthesia, epilepsy, brain attentiveness, sleep disorders, brain disorders, etc. EEG's are complex signals whose statistical properties depend on both space and time. Their randomness and non-stationary characteristics make them impossible to be described in an accurate way with a simple technique, requiring analysis and characterization involves techniques that take into account their non-stationarity. For that, new advanced techniques in order to improve the efficiency of the EEG based methods used in the clinical practice have to be developed.

The main objective of this thesis was to investigate and implement different methods based on nonlinear techniques in order to develop indexes able to characterize the frequency spectrum, the nonlinear dynamics and the complexity of the EEG signals recorded in different state of consciousness.

Firstly, a new method for removing peak and spike in biological signal based on the signal envelope was successfully designed and applied to simulated and real EEG signals, obtaining performances significantly better than the traditional adaptive filters.

Then, several studies were carried out in order to extract and evaluate EEG measures based on nonlinear techniques in different contexts such as the automatic detection of sleepiness and the characterization and prediction of the nociceptive stimuli and the assessment of the sedation level.

Four novel indexes were defined by calculating entropy of the Choi-Williams distribution (CWD) with respect to time or frequency, by using the probability mass function at each time instant taken independently or by using the probability mass function of the entire CWD. The values of these indexes tend to decrease, with different proportion, when the behavior of the signals evolved from chaos or randomness to periodicity and present differences when comparing EEG recorded in eyes-open and eyes-closed states and in ictal and non-ictal states.

Measures obtained with time-frequency representation, mutual information function and correntropy, were applied to EEG signals for the automatic sleepiness detection in patients suffering sleep disorders. The group of patients with excessive daytime sleepiness presented more power in θ band than the group without sleepiness, which presented higher spectral and cross-spectral entropy in the frontal zone in δ band. More complexity in the occipital zone was found in the group of patients without sleepiness in β band, while a stronger nonlinear coupling between the occipital and frontal regions was detected in patients with excessive daytime sleepiness, in β band.

Time-frequency representation and non-linear measures were also used in order to study how adaptation and fatigue affect the event-related brain potentials to stimuli of different modalities. Differences between the responses to infrequent and frequent stimulation in different recording periods were found in series of averaged EEG epochs recorded after thermal, electrical and auditory stimulation.

Nonlinear measures calculated on EEG filtered in the traditional frequency bands and in higher frequency bands improved the assessment of the sedation level. These measures were obtained by applying all the developed techniques on signals

recorded from patients sedated, in order to predict the responses to pain stimulation such as nail bad compression and endoscopy tube insertion. The proposed measures exhibit better performances than the bispectral index (BIS), a traditional indexes used for hypnosis assessment.

In conclusion, nonlinear measures based on time-frequency representation, mutual information functions and correntropy provided additional information that helped to improve the automatic sleepiness detection, the characterization and prediction of the nociceptive responses and thus the assessment of the sedation level.

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Chapter 1

Introduction

This first chapter introduces the concepts that have been addressed along the present doctoral thesis. Section 1.1 indicates the motivation that has given rise to this research. Section 1.2 describes some concepts related to electroencephalography and the main techniques used in its analysis, giving special emphasis on frequency domain and nonlinear dynamics techniques. Furthermore, the main advantages and disadvantages of each technique that were deduced from the literature review are described in this section. Sections 1.3, 1.4 and 1.5 describe the state of art of the studies concerning sleepiness assessment, nociception, sedation and anesthesia. Section 1.6 specifies the objectives and contributions achieved during the development of this thesis.

1.1 Motivation

This thesis is part of the issue related to the advanced analysis of EEG signals to assess different states of consciousness. Electroencephalogram (EEG) recordings provide insight into the changes in brain activity associated with various states of anesthesia, epilepsy, brain attentiveness, sleep disorders, brain disorders, etc. EEG's are complex signals whose statistical properties depend on both space and time. Their randomness and non-stationary characteristics make them impossible to be described with a simple technique such as the Fourier transform, in an accurate way. This increases the need to develop new advanced techniques in order to improve the efficiency of the methods that used EEG in the clinical practice, such as sleepiness detection, nociception, sedation and anesthesia assessment.

Excessive daytime sleepiness (EDS) is a socially and clinically relevant problem. According to one current definition, EDS is “the presence of sleepiness in a situation when an individual would be expected to be awake and alert” (Santamaria and Chiappa 1987; Makeig *et al.*, 1993; Jung and Makeig 1994; Gusnard *et al.*, 2001, Andrews-Hanna *et al.*, 2010, Vanhauzenhuyse *et al.*, 2010). EDS is a common symptom that can have many different causes. EDS occurring at least 3 days per week has been reported in between 4% and 20.6% of the population, while severe excessive daytime sleepiness was reported at 5% (Ohayon, 2008). Several researchers have attempted to use the EEG features for the development of automatic methods for detecting drowsiness (Wilson and Bracewell, 2000; Vuckovic *et al.*, 2000; Smith *et al.*, 2002; Lin *et al.*, 2005; Subasi and Erçelebi, 2005; Chiou *et al.*, 2006; Fu J *et al.*, 2008; Lin *et al.*, 2008, Swarnkar *et al.*, 2008; Yeo *et al.*, 2009; Johnson *et al.*, 2011; De Rozaro *et al.*, 2013). However, their algorithms involve procedures and results of mixed quality and weakness, suggesting that the automatic sleepiness detection still remain an open problem.

Currently, the administration of anesthesia is a highly prevalent process, reaching rates between 9 and 10 anesthetics per 100 inhabitants per year in countries like the United States and Spain (Sabaté 2006). The anesthetic state may be defined as the combination of pharmacological effects that minimize the impact of aggressive in surgical patients. The anesthetic state was proposed as a hierarchical model (Bouillon *et al.*, 2004) which examines the pharmacological relationship (Verotta *et al.*, 1989), the nociceptive response caused by surgery at peripheral level and muscle relaxation (Peñuelas-Acuña *et al.*, 2003), with the aim to maintain a dynamic

equilibrium at hemodynamic level (homeostasis) in the patient. To determine appropriate requirements for administration, monitoring and control of sedation and/or analgesia in invasive medical procedures is necessary in order to minimize the impact of the aggression in the patient and the implications on the outcome of the process. There is currently a significant importance in studies that establish a suitable drug combination and optimally control of sedation and analgesia. Typically, they are based on the development of predictive mathematical models that represent the physiological system responsible of pain (Smet *et al.*, 2008; Gambús *et al.*, 2011), and techniques to assess the level of analgesia (Luginbuhl, 2006; Rantanen, 2006; Storm, 2008; Jeanne, 2009), EEG monitor for the anesthesia level assessment (Sigl, 1994; Rampil, 1998; Jensen *et al.*, 1996; Litvan *et al.*, 2002; Viertiö-Oja *et al.*, 2004; Valencia *et al.*, 2012).

However, none of these methods has proven to be clinically useful because they are influenced by the response of the autonomic nervous system (ANS) and also sensitive to other disturbances, such as changes in blood pressure or heart rate due to patient's baseline condition (hypertension, arrhythmias of diverse etiology), sympathomimetic drug delivery or unpredictable situations such as perioperative bleeding. Furthermore, the EEG-based monitors cannot reliably distinguish between light sedation and deep sedation, as these are designed to measure levels of general anesthesia that handles very different levels of hypnosis to those used in sedation procedures. Additionally, the EEG signals recorded during sedation procedures contain more EMG components because patients develop a greater degree of mobility. Therefore, it still remains the need for a quantitative and objective measurement to quantify the level of sedation in patients undergoing invasive procedures (Chisholm *et al.*, 2006).

1.2 The Electroencephalogram

The brain is a very complex structure built up of neurons that communicate via electric impulses. When millions of neurons communicate at the same time, they give rise to an electric field that is even measurable from the scalp. Electroencephalography (EEG) is the measurement of the electrical activity of the brain by using electrodes placed on the scalp.

The EEG is the summation of microscopic ionic currents from the large population of underlying cortical neurons, for the most from pyramidal ones that have long straight dendrites perpendicular to the surface of the cortex. These dendrites receive a large number of synaptic connections from other neurons and, when these are activated synchronously, their individual current flows are summed. A larger current flow is resulting and this is able to generate voltage which can be detected as the EEG on the scalp. Because voltage fields fall off with the fourth power of the radius, activity from deep sources is more difficult to detect than currents near the skull.

Scalp EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency ranges, spatial distributions and are associated with different states of brain functioning (e.g., waking and the various sleep stages). These oscillations represent synchronized activity over a network of neurons. The EEG is classically divided into five different rhythms according to the frequency band of the signal. Their proportions in the signal depend on the subject's age and mental status (Table 1.1).

Table 1.1. Partition of the EEG in frequency bands

Band	Frequency (Hz)	Location	Description
δ	<4	Frontally in adults, posteriorly in children.	High-amplitude waves. Typically occurs during sleep. Indicative of brain disease and cerebral damage.
θ	4-8	Found in locations not related to task at hand.	Occurs when a person is drowsy, going to sleep or waking up. Higher in young children. Associated with inhibition of elicited responses.
α	8-12	Posterior regions of head, both sides, higher in amplitude on non-dominant side. Central sites at rest.	Predominant in awaked subjects in a relaxed or reflected state. Higher with eye closed. The amplitude of this rhythm is larger in the occipital regions. Associated with inhibition control, seemingly with the purpose of timing inhibitory activity in different locations across the brain.
β	12-30	Both sides, symmetrical distribution, most evident frontally.	Associated with an activated cortex. Low-amplitude waves.
γ	>30	Somatosensory cortex.	Related to an active process of information in the cortex.

1.2.1 EEG measurements

Hans Berger conducted the first measurements of electrical activity from the human brain (Berger, 1929). At that time, the recording equipment consisted of the string galvanometer for recording of the electrocardiogram. Apart from lack of sensitivity in this apparatus, Berger also had to tackle the problems of electrodes, and of artifacts. Already then, he investigated different materials, electrode positioning and fixation, and electrode impedance, providing guidelines that still relate to those of today. Quite accurately, he described the Electroencephalogram as oscillations with average duration of 90ms (α waves) and 35ms (β waves), and amplitudes of 70-150 μ V and 20-30 μ V respectively (Geddes, 1995).

Since the days of Berger and the verification of his recordings by Jasper and Carmichael (1935), electroencephalography has taken its place as a standard laboratory investigation in clinical neurophysiology and neurology. It is used in the diagnosis of brain pathology, e.g., epilepsy, sleep disorders, and disorders of the nervous system. EEG recording is also used extensively in psychophysiological research and in the testing of drugs (pharmacology) (Pryse-Phillips, 1997).

Nowadays, EEG registration generally consists of simultaneous measurement of multiple signals (sometimes more than 100 in EEG topography research), mostly recorded on the scalp. Electrographicography (recorded directly from the exposed cortex) and in-depth intracranial recordings using needle electrodes (e.g., in neurosurgery, epilepsy) are not discussed in this overview. Standardization of all aspects of EEG recording is difficult because of the diversity in illnesses and monitoring applications. Different protocols and different equipment regulations exist between hospitals for similar investigations. Entirely different procedures may be needed in one single patient (e.g., ambulant recording, laboratory recording, monitoring during surgery). The only readily accepted instrumentation standard is the international 10-20 system for scalp electrode placement (Sharbrough *et al.*, 1991; Oostenveld *et al.*, 2001). The 10-20 system describes how electrodes are located on the scalp (Figure 1.1). The location of the electrodes on

the front-back line is based on dividing the distance between the nasion and the inion over the vertex in the midline. There are five locations marked along that line: frontal polar “Fp”, frontal “F”, central “C”, parietal “P”, and occipital “O”. “Fp” is located at 10% of the nasion-inion distance, the second point, “F”, at 20% of that distance from the “Fp” and so on in 20% steps. Lastly, the distance between point “O” and the inion is again 10% of the whole distance. In order to differentiate electrode locations between left and right hemispheres, even numbers are used as subscripts for the right hemisphere and odd numbers for the left one (Figure 1.1). If necessary, additional more closely spaced electrodes can be added (Jasper, 1958; Sharbrough *et al.*, 1991). In contrast, when EEG monitoring is performed in the operating room or intensive care unit, often only a limited number of electrodes are used (2-4). In this case they are mainly located on the forehead.

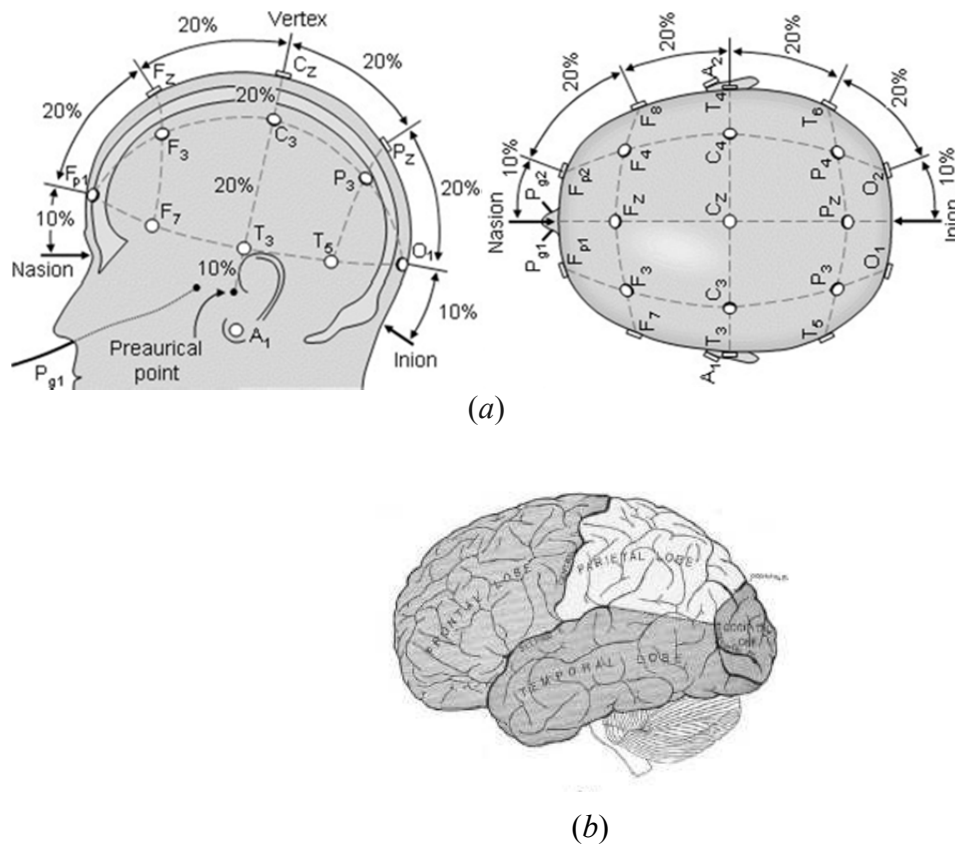


Figure 1.1. (a) 10-20 EEG electrode location system for EEG recording (picture adapted from van de Sharbrough *et al.*, 1991). (b) Location of the frontal, temporal, parietal and occipital lobes of the human brain (picture adapted from Gray, 2000)

1.2.2 Neurophysiology

The electrical activity elicited by single nerve cells stems from the electrochemical processes underlying the generation of ‘action potentials’, essential for information transfer between nerve cells. The neuron consists of a cell body, dendrites (afferent pathway) and axons (efferent pathway). A resting potential exists across the cell membrane, at an intracellular level of approximately -70mV . Neurotransmitters can change the permeability of the membrane mainly for sodium (Na^+) and potassium (K^+) ions. An increased ion influx causes depolarization of the membrane, resulting in a further change in permeability (the Hodgkin cycle: Kandel *et al.*, 1991). This process can trigger an ‘action potential’ wave that travels along the axon towards

other neurons. At the 'synapse', the contact point between axon and dendrite, the transmission of the nerve impulse occurs. Thus, processes in other cells are affected.

Postsynaptic potentials can be of excitatory or inhibitory nature, respectively causing a reduction (depolarization) or increase (hyperpolarization) of the membrane potential. These EPSPs and IPSPs are the primary origins for the EEG recorded from the scalp. Because EEG recording electrodes are relatively far from the source of these neuron potentials, the actual potentials of the EEG on the skull are approximately 100 to 1000 times smaller than intracellular levels. Moreover, the recorded activity on one electrode on the scalp represents the averaged behavior of about one million neurons in the cortex (of the approximate 100 billion in the brain). Large amplitudes in the EEG therefore require synchronous rhythmic activity in such neuronal populations. The rhythmic activity (especially α rhythm) has its origin in the thalamus, a deep structure of the brain, and is modified by dynamic feedback loops of inhibition and excitation (Schmidt, 1985; Lopes da Silva, 1987; Fischbach, 1992). The dynamic behavior, or rhythms, of electrical activity recorded from the brain can be classified by amplitude and frequency. Action potentials at the cellular level can be recorded at amplitudes up to 100mV. EEG phenomena recorded on the scalp range in amplitude between 1 μ V up to 200 μ V.

1.2.3 Recording equipment

EEG recordings using scalp electrodes are the most common. The skin below the electrode acts as impedance during the measurement, and is higher for low frequencies. Electrode impedance should be less than 5k Ω at 10Hz, and equal impedance on all electrodes should be ensured. Skin impedance can be reduced by proper preparation of the skin: scrubbing with a special paste or a blunt needle is common practice. Electrode leads should be as short as practically possible.

Classical types of EEG electrodes are metal cup electrodes, of silver/silver-chloride or gold, because of their favorable electrochemical properties. Newer self-adhesive electrodes or needle electrodes still have practical disadvantages, e.g., lasting visible marks on the skin, undesired sterilization procedures (Neuman, 1995; Litscher *et al.*, 1996). Because of drying of electrode paste and conductive gel electrode impedance will increase. Even worse, loose electrodes may result from patients moving their heads (e.g., during sleep). Firm fixation of electrodes is achieved using glue (collodion) and adhesive pads. Especially in prolonged EEG monitoring, regular electrode (impedance) checks should be part of the recording protocol. Some of the requirements are outlined below; more information is found in Spehlmann's EEG primer (Fisch, 1998).

The system must be equipped with a sufficient number of input channels, with high input impedance (at least 10M Ω). Calibration pulses at microvoltage levels (e.g., 50 μ V) should be available to check the voltage scaling on screen or paper. Electrode impedance checks must be available for all electrode channels. This facility must be highly accurate and allow for checks at different frequencies (0 to 1000Hz), at very low electrical currents through the electrodes during this measurement (below 10 μ A).

The common-mode rejection ratio of the amplifier must be sufficient to suppress noise and interfering signals synchronized at different electrode positions. At all possible input frequencies, a rejection ratio of 1/10000 or better is preferred. The common-mode rejection is altered when electrode impedances are not equal, which notably affects a bipolar recording. In this type of recording, the EEG is measured as the potential difference between the signal electrode and a 'reference' electrode with reference to a third electrode: the ground electrode

(connected to the signal ground on the amplifier). In a true unipolar recording, the reference electrode and ground electrode are one. In practice, a virtual reference electrode may be obtained by deriving the ‘common average’ of all electrodes (e.g., Goldman, 1949). The difference in noise between signal electrode and reference electrode will be amplified in unipolar recordings, whereas ‘common noise’ at bipolar recording positions is not measured, provided that the amplification is equal at both signal and reference electrode.

Several aspects are related to digitization of the EEG. First of all, the sampling frequency (f_s) should be at least 100Hz for normal EEG recordings. An anti-aliasing low pass filter must be applied with a cut-off frequency well below the Nyquist frequency (half of the sample frequency), and a decay of 6 or 12dB/octave. A steeper decay can result in distortion of spikes and sharp waves near the cut-off frequency, and is therefore not advised (Spehlmann, 1981). Aliasing is the effect that occurs when band limiting was inadequate, e.g., a 50Hz noise component can corrupt the spectrum at a lower frequency of 30Hz for $f_s = 80\text{Hz}$ (Mainardi *et al.*, 1995).

The input range of the amplifier must be sufficient to record the normal amplitude range of the EEG. However, the amplifier’s range should not be too small as it is often desirable to identify high amplitude artifacts. In this respect, the sensitivity or signal resolution must be adequately chosen for the application. Modern digital EEG equipment commonly uses 16-bit precision. For an input range of 2mV (i.e., $-1000\mu\text{V}$ to $+1000\mu\text{V}$), 12-bit samples can represent the EEG at approximately $0.5\mu\text{V}$ resolution (72dB), versus $0.03\mu\text{V}$ resolution in 16-bits (96dB). Standardization is extremely important to exploit fully all advantages of the new technology. Standardization of storage formats will greatly facilitate the exchange of EEG data (Kemp *et al.*, 1992), which will advance the development and testing of (new) algorithms. An outline of practical design principles for digital EEG can be found in Lesser *et al.* (1992), Gorney (1992) and Burgess (1993).

1.2.4 EEG artifacts

The EEG signal is very susceptible to a variety of large signal contamination such as power line noise, biological or electrode artifacts. These artifacts represent changes associated to cerebral activity that should be removed by filtering before further signal analysis. An important issue for recording of high quality EEG signals is artifacts prevention. Another approach to identify contaminations in the EEG is the direct monitoring of the source or external cause of the artifact. Separate recording devices may be needed to allow for retrospective identification of artifacts, e.g., the switching of electrocautery during surgery, or the sound levels of snoring during sleep. Proper annotation during the recording, or registration of such signals by means of event recording should be incorporated in the procedure (Lesser *et al.*, 1992). However, contamination of EEG data can occur at many points during the recording process. Improving technology can decrease externally generated artifacts such as line noise, but biological artifact signals must be removed after the recording process. Although in general it is possible to recognize and distinguish artifacts of physiological origin, one should keep in mind the possibility of artifacts simulating EEG activity. For instance, part of the frequency characteristics of muscle artifact lie within normal EEG frequency range. The main artifacts are outlined below, considering their non-physiological and physiological origin:

- *Artifact of non-physiological origin*

Electrode artifacts are more frequent when the electrode impedance increases during the recording of the EEG. But also the electrode head box and electrode leads are possible sources of artifact. For this, leads should not be curled and not be touched during the recording.

Electrodes and leads may pick up 50Hz (or 60Hz) sine wave patterns from the main power supply or other equipment, thus obscuring the EEG (Figure 1.2). Somewhat less severe mains interference is often caused by unequal electrode impedance at different positions, or by improper grounding of patients (Spehlmann, 1981). However, correct grounding may conflict with electrical safety regulations in some situations, e.g., in the operating room.

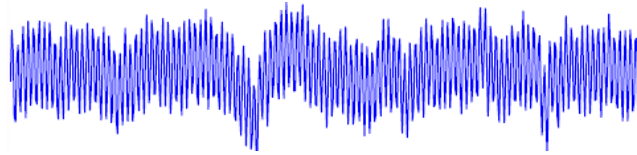


Figure 1.2: 50 Hz artifact in the EEG (Knight, 2003)

A characteristic artifact is the ‘electrode pop’, which is due to a sudden change in electrode contact resulting in a sharp spike in the recorded signal. Other artifact is the DC drift, or base-line swaying artifact, which is related to changing electrode impedance or caused by movement of leads. Most often this causes very low frequency patterns in the recorded EEG, and therefore may be adjusted by (temporarily) decreasing the time constant of the recording equipment (when other adjustments failed).

A whole range of electrical apparatus can cause mains interferences when electrical shielding or grounding is insufficient. Care has to be taken in the placement of patient and equipment, shielding for existing and possible electrical fields. The electrical field around power cables, transformers, and antenna-equipped devices can possibly be picked up on electrode leads. During surgery, electrocautery by the surgeon generally causes high amplitude, high-frequency artifact in the EEG. Other machinery, e.g., respirators, perfusion pumps, and other (mechanical) actuators such as flush devices, cutting, drilling, suctioning, rubbing and washing can cause (rhythmic) artifacts. Spikes may be introduced by malfunctioning recording equipment, especially when high sample frequencies are used and data acquisition boards have to operate at performance limits.

- *Artifact of physiological origin*

Large signal disturbances can occur in the EEG from muscle activity (Figure 1.3), i.e., movement of the head, body and limbs, or from tension in the facial muscles, or from the tongue or jaw (Klass, 1995). While undesired movement of a subject in an experimental setting can be prevented mostly by clear instructions, involuntary movements or anxiety are often difficult to suppress (e.g., muscle tremor, shivering). Sustained muscle artifacts are caused by muscle tension in the face (e.g., frowning), neck, and also on the scalp (smaller in amplitude), or by repetitive actions such as talking, or chewing and swallowing while eating (large amplitudes).

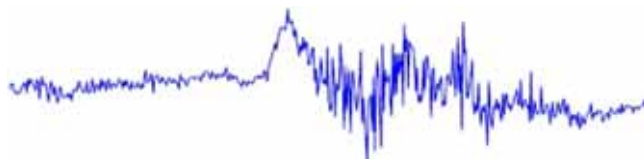


Figure 1.3: Muscular artifact in the EEG (Knight, 2003)

The eye acts like an electrical dipole in EEG recordings, being positive at the cornea, negative at the retina. Eye-artifacts are most prominent during REM sleep, but can also contaminate the EEG during drowsiness or light sleep. In awaking state, blinks of the eye consist primarily of eyelid movement, which causes less significant artifact than movement of the eyeball. However, rhythmic activity (α range) can be observed in the EEG because of fluttering of the eyelid. The effect of the eye-blink generates high-amplitude potentials that can be in the millivolt range consisting mostly of low frequency activity, and is distinctly observed in the EEG recorded from anterior (especially prefrontal) positions on the scalp (Figure 1.4).

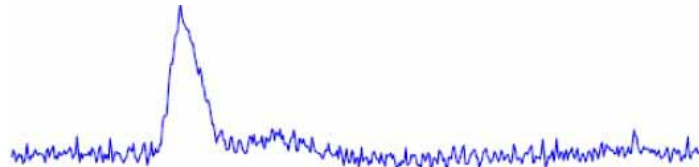


Figure 1.4. Eye blink artifact in the EEG (Knight, 2003)

Electrical activity from the heart can appear in the EEG, especially during recordings of very low voltage. Artifacts originating from the heart or circulatory system are sometimes caused by inadequate electrode placement. It is picked up more easily in the EEG recorded from wide inter-electrode distances, especially across the head to the left ear, and in subjects with short necks. Alternative reference electrode placement can be used to reduce this type of artifact (Spehlmann, 1981; Barlow, 1986).

The actions of the respiratory system can also cause some low frequency artifact in the EEG signals as recorded on the scalp because of the rhythmic movement of the chest, neck, and head. Excessive artifact from respiration effects may be observed during snoring.

Sweating is the main cause of the artifacts in the EEG originating from changes in skin impedance (electrodermal artifact). Sweat can also affect the conductive properties of electrodes through dissolving of the electrode gel. In the recorded signal on the scalp this will cause lasting effects when the electrode impedance eventually becomes too high (e.g., interference artifact, or slow rhythmic swaying of the base-line DC levels).

1.2.5 Existing methods for artifact processing

Rules for artifact detection are often based on amplitude thresholds that have been determined empirically. For instance, in the research of Flooh *et al.*, (1982) an artifact was defined as the EEG amplitude exceeding a threshold six times the average amplitude of the preceding 10 seconds. Still, max-min amplitude criteria are often selected because of simplicity (Kirkup *et al.*, 1997). Although fixed amplitude thresholds may be used as a basic procedure, they can be very unspecific in the identification of certain artifacts (Verleger, 1993). Another very basic time domain procedure for correction of artifacts is subtraction of the average amplitude to correct for DC offset or base line swaying. Several successful studies were mentioned by Barlow (Barlow, 1979; Barlow, 1986) in which the first derivative or slope, as well as the second derivative was applied in the detection of fast activity. The most commonly used approaches for artifact removal are filters mainly based on adaptive algorithms with linear and nonlinear structures (Haykin, 1996; Lym, 1997). Filtering specific frequency bands from the EEG can be used to reduce muscle activity or main interference. Special cables, leads and filters

can be used to reduce (50/60Hz) interference artifact. Muscle artifact is generally characterized as a relatively high-frequency phenomenon. However, heavy low pass filtering, using a cut-off frequency as low as 12.5Hz, is necessary to make sure that residual muscle activity cannot resemble EEG β activity. Obviously, this is not desirable in most recordings, because true β activity and spike-type activity will be attenuated or even obscured. In order to correct or remove ocular artifacts from EEG, many regression-based techniques have been proposed (Whitton *et al.*, 1978; Verleger *et al.*, 1982; Gratton *et al.*, 1983; Woestenburg *et al.*, 1983; Kenemans *et al.*, 1991). They require calibration trials in order to estimate the EOG component from each of the EEG channels and then they remove it by subtraction. Independent component analysis (ICA) represents an efficient way (Jung *et al.*, 2000; LeVan *et al.*, 2006) to perform EOG signal separation from the EEG signals. Several methods for dealing with ocular artifacts in the EEG were reviewed by Croft *et al.* (2000), focusing on the relative merits of a variety of EOG correction procedures. A noise cancellation method based on adaptive filtering was implemented by He *et al.* (2004) with the aim of removing ocular artifacts from on-line EEG without calibration trials but using the EOG signal as reference.

1.2.6 Time-domain analysis of the EEG

Amplitude histograms of the EEG often show a symmetrical, essentially Gaussian distribution. The characteristics of Gaussian distribution can be summarized by calculating the amplitude mean and standard deviation measures, which can be used to characterize the EEG in time-domain. Almost all EEG processing is based on parametric modeling of periods in the EEG time series. The investigated periods should more or less have constant statistical properties to validate such ‘epoch based’ parameter extraction. The derived features of EEG epochs are often hypothesized to follow a Gaussian, or normal distribution; this is usually taken as a requirement for stationarity. Different statistics have been developed to test the hypothesis theoretically, both in the frequency-domain and in the time-domain (Moulines *et al.*, 1993). The latter domain is preferred for stationarity testing of short epochs, because of reduced frequency resolution in small sample sizes (Lilliefors, 1967).

In signal theory, stationary stochastic processes are defined as processes whose statistics do not change in time (Cohen, 1995a). Theoretically, this can only be tested in an ‘ensemble of (multiple) realizations of the same process, and can therefore not be implemented in a real-life signal. In order to overcome the impossibility of ensemble testing, the signal is often assumed to be ‘ergodic’. Ergodicity relates to processes in which every sequence or sizeable sample is equally representative of the whole. In practical terms, it can be denoted that a stationary signal must have several time-invariant properties, requiring explicitly more than just one feature to describe the EEG signal (Salden, 1997).

1.2.7 Frequency-domain processing

The EEG power spectrum is usually calculated by power spectral density (PSD) methods such as Welch’s method of averaged modified periodograms. Epochs are divided into segments with or without overlap; different windows are usually applied to each segment before applying the Fourier transform. The final spectral density is achieved as the average of spectral densities of all the segments. Longer segments provide better frequency resolution, but then restrict time resolution; and too lengthy segments may not be stationary. The spectral power in each band (P_{δ} , P_{θ} , P_{α} , P_{β}) can be calculated as the area under the PSD curve normalized by the total PSD

area. Also the mean frequency (mF) in each band as the centroid of the PSD curve is used to describe the EEG spectrum.

A parameter that quantifies one aspect of frequency characteristics is the ‘spectral edge frequency’ or SEF (Rampil *et al.*, 1980). SEF is defined as the highest frequency at which a significant amount of energy is present in the EEG (usually calculated at 50% or between 75 and 95% of total power contents). The SEF50 represent the value of the median frequency of the spectrum ($medF$).

1.2.8 Time-frequency analysis

Since the Fourier transform is based in comparing the signal with complex sinusoids that extend through the whole time domain, its main disadvantage is the lack of information about the time evolution of the frequencies. Then, it also needs the requirement of stationarity in order to avoid alteration that might occur at some time boundary affecting the whole Fourier spectrum. On the contrary, time-frequency representation (TFR) permits to observe the evolution of the periodicity and frequency components with respect to time, allowing the analysis of non-stationary signals.

Different time-frequency analysis methods have been proposed for analyzing, interpreting and scoring the EEG signal in the last decades such as Wigner and Choi-Williams distributions belonging to Cohen class (Cohen, 1995b) distributions, wavelets (Sitnikova *et al.*, 2009) or Hilbert Huang transform (Huang *et al.*, 1998). The main properties of the Wigner distribution such as marginality, instantaneous frequency and group delay make this distribution well suited for the purpose of this thesis. However, the interfering terms, which affect this distribution, alter the interpretation of the spectrum at each time instant. The Choi-Williams distribution (CWD), which has the same properties of the Wigner distribution, is able to eliminate these terms. In this way, these properties allow CWD to be considered as the spectral density of a signal at each time instant. Wavelet techniques are mostly used for detection of known waveforms in a noisy background signal. However, the application of wavelets implies the choice of the right type of mother wavelet function. The Hilbert Huang transform, that is based on the Empirical Mode Decomposition (EMD) (Rehman, 2010), is very sensitive to the instantaneous energy content of the different harmonics and depends on the spline-fitting techniques and stopping criterion chosen (Li *et al.*, 2008) that can perturb the interpretation of the result (Wacker and Witte, 2013), especially if random noise is present in the signal. Furthermore, in the frequency representation provided by the wavelets and the Hilbert Huang transforms there is not a direct correspondence between scale and wavelength or frequency. The conversion factors for selecting frequency that yield an approximate scale-frequency correspondence must be found. Since this would represent an additional difficulty in the interpretation of the results, CWD was selected in this thesis as the optimal (Wacker and Witte, 2013) method for the time-frequency representation of the EEG signals.

1.2.9 Nonlinear analysis of EEG

Different studies proposed that the EEG can be adequately described with methods from nonlinear dynamics. Entropy is a mathematical concept to quantify nonlinear dynamics. However, there are many different ways of defining complexity and entropy, and even more ways of calculating them. In the EEG analysis today, different properties of the signal are used to estimate entropy and the results are compared with one another in the literature. The fundamental

assumption of nonlinear techniques is that EEG signal is generated by nonlinear deterministic processes with nonlinear coupling interactions between neuronal populations. Nonlinearity in the brain is introduced, even at the cellular level (Andrzejak *et al.*, 2001), since the dynamical behavior of individual neurons is governed by threshold and saturation phenomena, large networks of interconnected neurons are likely candidates for self-organized criticality, which refers to large systems with local nonlinear interactions in which a slow build-up of some energy value is alternated with brief bursts of energy redistribution (Stam *et al.*, 2005). In general, the most applied complexity measures found in the literature are attractor dimension (Walling *et al.*, 2006), correlation dimension (Lalitha *et al.*, 2007), Lyapunov exponent (González *et al.*, 2009), fractal dimension (Ferenets *et al.*, 2006) and entropies (Ferenets *et al.*, 2006). All complexity measures mentioned above depend on the setting of estimation parameters, namely embedding dimension, time delay of phase space reconstruction, prediction time horizon, and partitioning signals. Assuming that the dimensional complexity of the nonlinear system that generate the EEG signals is expected to be between 5 and 10 (Jing *et al.*, 2000; Pereda *et al.*, 1998), depending on the aware or unaware states, the limit of the time series length was defined between 10^3 and 10^5 samples (Eckmann *et al.*, 1992) or even above than 10^5 (Theiler *et al.*, 1990). These suppose a large sample size of the data while mutual information function that describes the amount of information of a signal with regard to a time shifted quantity can be constructed on short time series. On the other hand, mutual information requires the estimation of probability distribution; also in this case, if the EEG time series have limited length, this estimation might be affected, generating wrong mutual information values. However, the low limit of the series length for mutual information computation has been fixed to about 500 samples (Hoyer *et al.*, 2006), and furthermore in previous works mutual information functions were estimated with time series with length between 10^3 and 10^4 samples (Hoyer *et al.*, 2005; Hoyer *et al.*, 2006; Jeong *et al.*, 2001). Auto-mutual information function (AMIF) is calculated as the mutual information between two measurements taken from a single time series at different time-scales. In a previous work, this function applied to EEG from Alzheimer's disease (AD) patients showed that a more slowly decrease along time delays is associated with a more regularly EEG signal (Abásolo *et al.*, 2008).

A new concept recently introduced by Principe *et al.* (2006) is correntropy, used to quantify similarity using the higher order statistics in random processes based on a reproducing kernel Hilbert space (RKHS) method (Santamaria *et al.*, 2006). By nonlinearly transforming the random processes into a high dimensional RKHS and computing the conventional correlation on the transformed signals, correntropy is sensitive to both the higher order statistical distribution information and temporal structure of the original random process. The ability to reflect nonlinear characteristics of the signal makes correntropy a well-qualified candidate for characterization of nonlinear dynamics. Another attractive property of the correntropy function is its robustness against impulsive noise. Besides that, the use of kernel methods makes the correntropy computationally efficient since it can be computed directly from the data.

1.3 Sleepiness assessment using EEG

In the clinical practice, EDS is considered a key factor for CPAP treatment (Strollo, 1996). However, there is no simple method to evaluate EDS. Subjective scales are easy to perform but correlate poorly with objective measures (Chervin, 1999, Kerdenzka, 2013), and it is well known that sleepiness may be easily confounded with fatigue, or depression related symptoms (Chervin, 2000). The multiple sleep latency test (MSLT) (Carskadon, 1986) and the

maintenance of wakefulness test (MWT) (Doghramji *et al.*, 1997) are the most commonly used laboratory-based methods for objective characterization of the ability and the resistance to fall asleep, respectively (Littner, 2005). These tests are complex and expensive to perform on daily routine. Thus, there is a need to develop new methods to easily evaluate objective EDS.

Recently, new studies have reported that sleepiness could be measured with simpler methods that process, for instance, the oculo-motor activity (Fabbri *et al.*, 2010, De Gennaro *et al.*, 2005) or the autonomic nervous system (ANS) activity (Chua *et al.*, 2012, Lombardi *et al.*, 2008). On the other hand, electroencephalogram (EEG) recordings provide insight into the changes in brain activity associated with various states of arousal from sleep to waking and is often used as the “gold standard” in the identification of states ranging from vigilant and alert to drowsy (Santamaria and Chiappa, 1987) or asleep. Changes in the frequency and amplitude of the EEG correlate directly with behavioral performance measures (Jung and Makeig, 1997) and changes in alertness and awareness (Makeig *et al.*, 1997).

Several researchers have attempted to leverage these characteristics for the development of EEG based drowsiness algorithms using EEG feature extractions (Johnson *et al.*, 2011), EEG power spectral density (PSD) bandwidth comparisons (Lin *et al.*, 2008, Swarnkar *et al.*, 2008), increases of event related potential latencies (Smith *et al.*, 2002), linear regression (Chiou *et al.*, 2006), stepwise linear discriminant functions, artificial neural networks (Subasi and Erçelebi, 2005), principal component analysis (Fu J *et al.*, 2008), linear regression models (Lin *et al.*, 2005), etc. Furthermore, Wilson and Bracewell (2000) developed a method for detecting the alert state by applying wavelet-based preprocessing and artificial neural network (ANN); Vuckovic *et al.* (2002) used ANN as an automatic classifier of alertness and drowsiness from EEG recordings on arbitrary normal subjects. Khushaba *et al.* (2001) develop an efficient fuzzy mutual-information-based wavelet packet transform feature-extraction method for classifying the driver drowsiness state into one of predefined drowsiness levels. More recently, Yeo *et al.* (2009) applied support vector machines (SVM) as a classification tool to process EEG data for the detection of driving drowsiness. However, these algorithms present methodologies and results of mixed quality and weakness as small sample size, non-inclusion of sleep disorders, lack of cross-validation analysis, task dependence/specificity, algorithm complexity, large number of channels required and comparison with manual classification of EEG data that include consistency problems. Moreover, the study of sleep onset while driving differs from normal sleep studies as the passage from wakefulness to sleep is resisted and the subject struggles to maintain vigilance. Furthermore, since many features of EEG signals cannot be generated by linear models, it is generally argued that nonlinear measures are likely to give more information than the ones obtained with conventional linear approaches. For example, De Rozaro *et al.* (2013) suggest that the DFA scaling exponent correlates with impaired performance and increased sleepiness in obstructive sleep apnea patients. However, their results might be influenced by the differences in the age and body mass indices between the two groups studied. Additionally, Papadelis *et al.* (2007) used spectral and entropy measures applied to EEG and EOG as a neurophysiological indicator of driver sleepiness, demonstrating their potential of monitoring sleepiness.

1.4 Evoked potentials and Nociceptive Response

With event-related brain potentials (ERPs), the neural basis of perception and cognition can be investigated with high temporal resolution. While ERPs do not reveal accurate information on the loci of activated brain areas, they do provide temporally high information on

the various stages of information processing and the neural components associated with perception.

One component belonging to the family of cognitive ERPs is the mismatch negativity (MMN) (Näätänen *et al.*, 1978; Näätänen, 1992, 1990; Picton, 2000). The research using MMN has shed light to auditory sensory memory processes, resolution of the auditory system in discriminating sound features, as well as to impairments in these processes. While the MMN has originally been observed and thereafter intensively studied in the auditory modality, some reports suggest that it can be elicited also in the visual (Tales *et al.*, 1999; Czigler *et al.*, 2004; Pazo-Alvarez *et al.*, 2003) and tactile (Kekoni *et al.*, 1997; Shinozaki *et al.*, 1998; Akatsuka *et al.*, 2005) systems. Yet, the theory on the MMN is primarily based on the empirical evidence obtained in the auditory modality. Besides electrophysiological means, MMN has been recorded also with other methods, like magnetoencephalography (MEG) (Hari *et al.*, 1984), positron emission tomography (PET) (Tervaniemi *et al.*, 2000; Müller *et al.*, 2002), optical imaging (OI) (Rinne *et al.*, 1999), and functional magnetic resonance imaging (fMRI) (Opitz *et al.*, 2005; Mathiak *et al.*, 2002; Doeller *et al.*, 2003; Molholm *et al.*, 2005). Traditionally, the MMN has been recorded in the so-called oddball paradigm, in which repetitive sounds (frequent) and rare occasional deviant sounds (infrequent) are presented. The repetitive sound forms a memory trace in the auditory system, and if a new sound does not match this memory trace, the MMN is elicited after about 100–250 ms (Näätänen, 1992; Näätänen and Winkler, 1999). This indicates that the auditory system was able to distinguish between these two sounds. It has become evident that the MMN reflects even more complex auditory processes than only those related to the discrimination of physical features of sounds. In fact, the MMN reflects a deviation from the preceding stimulus events or regularities rather than merely the deviation from static stimulus properties (Saarinen *et al.*, 1992; Tervaniemi *et al.*, 1994; Paavilainen *et al.*, 1998; Näätänen and Winkler, 1999; Näätänen *et al.*, 2001; Paavilainen *et al.*, 2001). These findings on the MMN's nature in auditory cognition have important implications in understanding, for example, to what extent complex information can be processed without attention.

Several cerebral sources have been reported for the MMN, each of which probably having a specific role in early cognition. One MMN source is in the frontal areas, proposed to be involved in the attention switch after the sound change has been analyzed in the temporal lobes (Giard *et al.*, 1990; Rinne *et al.*, 2000). In addition, MMN generators have been reported in the parietal lobe (Lavikainen *et al.*, 1994; Levänen *et al.*, 1996) and subcortically (Csepe, 1995). Although attention can modulate MMN amplitude under particular circumstances, MMN is elicited even when the subject is not attending to the stimuli (Woldorff *et al.*, 1998; Näätänen, 1991). In fact, the MMN elicitation may lead to an attention switch towards a sound change in an unattended environment if the infrequent sound is disturbing.

The most recent studies have provided evidence that even complex, temporal, linguistic stimulus features and long-term learning effects are reflected in MMN responses, thus significantly broadening the theoretical scope of the MMN research. MMN can be used to identify speech-perception problems in newborns and infants well before they manifest themselves in the form of speech delay, predict coma outcome, estimate the function of cochlear prostheses, and evaluate the pathology of auditory processing in schizophrenia, neurodegenerative diseases and aging.

Although MMN is most often examined with auditory stimuli, there are also reports on MMN to somatosensory stimuli (Tesché *et al.*, 2000; Fischer *et al.*, 2006). Precisely, pain is a symptom that interferes with processing of inputs from other sensory modalities (Casanova *et al.*, 2011) and, therefore, it seems reasonable to examine how the brain processes nociceptive inputs. In neuropathic pain, damage of nerve fibers may lead to abnormalities in the nociceptive

evoked potentials (nEPs), while in nociceptive pain the nEPs are usually normal. Unfortunately, though, many patients have the two forms of pain and conventional neurophysiological studies are only of limited help. The MMN component is frequently hidden by noise at various frequency bands generated by different neuron activities. It is currently hard to characterize with quite high accuracy this component during electric stimulation and no studies have been published so far on MMN generated by thermal stimulation. As an example, electric and thermal responses to frequent and infrequent stimuli can be seen in Figures 1.5 and 1.6.

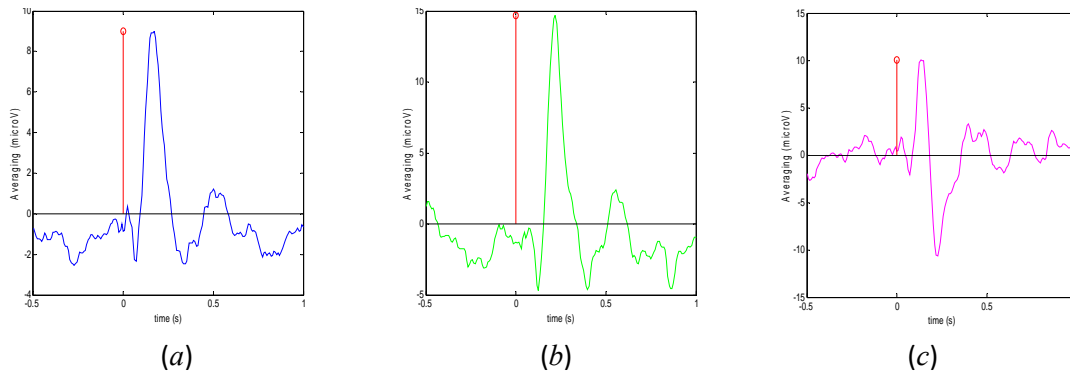


Figure 1.5. Averaged EEG responses to electric stimuli: (a) frequent; (b) infrequent; (c) MMN; difference between frequent and infrequent

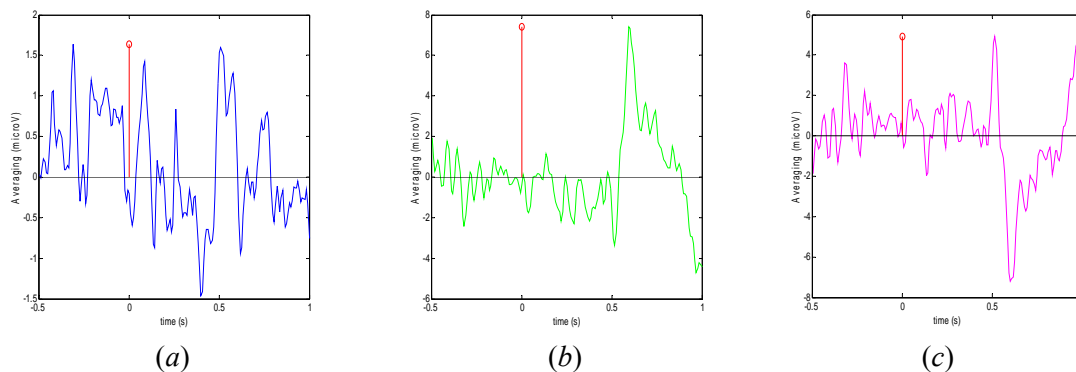


Figure 1.6. Averaged EEG responses to thermal stimuli: (a) frequent; (b) infrequent; (c) MMN; difference between frequent and infrequent

Regarding the application of TF representation in precedent ERPs studies, it was mostly used in order to measure the peak time, peak frequency and peak power of windows of EEGs containing stimuli response. It is known that TF analysis can separate the useful information from noise in TF space in order to avoid the variability caused by noise. Zhang *et al.* (2010) showed that ERP signals present a single and definite component in TF space. This TF component was found to remain stable during surgery if there are no changes in the status of neurological function. To identify the ERP peak in TF distributions is therefore simple and convenient. TF analysis of ERP is also advantageous in that it represents the features of a whole waveform, not only an initial curve or peak. In addition to the generally measured initial peak of ERP signals, there are some sub-waves which contain information regarding nervous system function. The use of the entire waveform in calculation of the peak power may explain its stability in comparison with the amplitude, which relies only on the height of one peak in the waveform. TF analysis of ERP signals shows a single peak in a certain time-frequency space, which are easily identified and measured.

It was found that MMN can be promising candidates for predicting outcome. A meta-analysis of Daltrozzo *et al.* (2007) indicated that MMN appeared to be reliable predictors of awakening in low-responsive patients with stroke or hemorrhage, trauma and metabolic encephalopathy etiologies. For these reasons, the optimization of the study of MMN response can be useful in order to apply it in the characterization and prediction of the pain response during sedation.

1.5 Anesthesia and sedation

The administration of anesthesia is highly prevalent among the general population. Only in Catalonia over 600000 anesthetics are performed annually (with an annual rate anesthetics/population of 9/100), that gives an idea of the importance of the anesthetic process among the general population. Anesthesia is defined as the state of unconsciousness, amnesia and hemodynamic, motor, and endocrinologic stability during surgery, produced by specific medication (van Gils, 2002). This means that for achieving an adequate level of anesthesia, usually a combination of hypnotic, analgesics, and neuromuscular blocking agents are used. Therefore, general anesthesia consists of three partially dependent components. A short description is given subsequently and in figure 1.7.

Hypnosis: with the use of hypnotic medication, the patient is taken to the unconscious state and he is unaware of ongoing events. Hypnosis is a crucial component of general anesthesia guaranteeing the patient to be unaware of the ongoing events and have no memories of the intraoperative period. It can be induced by affecting the neural activity of the brain using either intravenous (IV) anesthetics, such as propofol, or inhaled anesthetics like isoflurane, sevoflurane, and desflurane. Most of the hypnotic agents act in the central nervous system (CNS) by either increasing the transmission of the primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or by decreasing the activity of the glutamate-driven primary excitatory N-methyl-D-aspartate (NMDA) receptors (Århem *et al.*, 2003).

Analgesia: painless is obtained with the use of analgesic medication. Despite the fact that the patient could be in deep hypnosis, his body can still perceive the pain (nociception). The purpose of analgesia is to suppress the perception of pain and hemodynamic responses to noxious stimulation. As many of the hypnotic drugs have poor analgesic properties (Vuyk *et al.*, 1995), a separate drug for this purpose is often coadministered. Nowadays, a common practice is to combine an opioid with the hypnotic agent to improve the quality of anesthesia (Lichtenbelt *et al.*, 2004). Opioids, such as morphine, fentanyl, and remifentanyl act through specific receptors located in the brain and spinal cord (Mansour *et al.*, 1995). The analgesic effects of opioids arise from their ability to inhibit the transmission of nociceptive information from the spinal cord to the brain, as well as their direct influence on the pain perception in the brain (Fukuda, 2005).

Muscle relaxation: The relaxed state of muscles is often required for the surgeon to perform an operation, it is usually obtained either by the use of neuromuscular blocking agents or sufficient combination of hypnosis and analgesia.

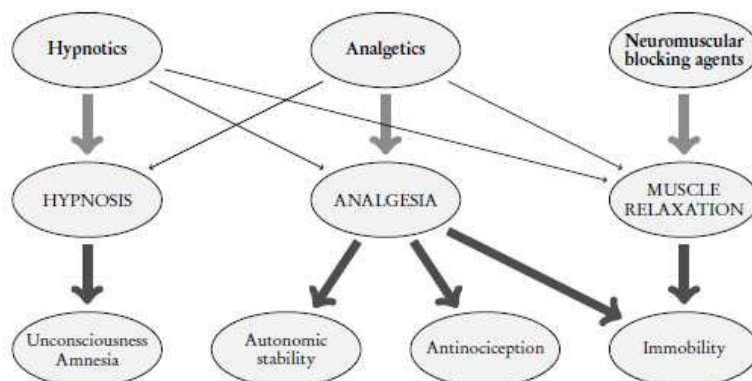


Figure 1.7. Scheme of drug-effect relationship (Diagram adapted from Van Gils, 2002)

The aggression that occurs in patients undergoing surgery triggers a series of responses in the body, both in physiological level as tissular that may have implications on the final outcome of the surgical process. To mitigate the intensity of these responses a certain level of protection or anesthetic state must be reached. The anesthetic state can be defined as the combination of pharmacological actions that minimize the impact of surgery aggressiveness and composed of hypnosis, analgesia and immobility, and autonomic and hemodynamic stability (Figure 1.8). To achieve an appropriate level of hypnosis, hypnotic drugs should be used; for the level of anesthesia, potent opioid predominantly highly synergistic with hypnotic drugs; and immobility may require the administration of neuromuscular blocking drugs. Propofol is the most frequently used intravenous anesthetic today (Reves *et al.*, 2005). It is utilized in the operating room and intensive care unit (ICU) for both induction and maintenance of anesthesia. These are carried out using either repeated boluses or continuous drug infusion. When delivered to the circulation, propofol is rapidly metabolized in the liver to water-soluble compounds, which are then excreted in the kidneys (Simons *et al.*, 1985). Propofol is primarily a hypnotic agent resulting in unconsciousness and amnesia swiftly after beginning of administration. Remifentanyl is an opioid increasingly used in the operating room and intensive care (Fodale *et al.*, 2008). Intra-operatively, it is given to patients as a supplement to hypnotic drug, or alone in high-dose opioid anesthesia (Servin 2003; Coda, 2009). The pharmacodynamic properties of remifentanyl are similar to all opioids representing strong μ -receptor agonism (James *et al.*, 1991). By this mechanism, it selectively decreases the amount of pain and discomfort during surgical procedure (Laitinen and Salomäki, 1999).

For several years, a number of methods have been developed for the noninvasive assessment of the level of consciousness during general anesthesia. From the classic assessment of the hemodynamic response, Bouillon *et al.* (2004) proposed hierarchical model of the anesthetic state that was developed in detail by Stanski *et al.* (2004). Through methods that analyze plethysmographic response (Luginbuhl *et al.*, 2007) or more recently the surgical stress index (SSI), initially developed as a multiparameter indicator but lately only based on heart rate variability (HRV) and on the analysis of pulse wave (Rantanen *et al.*, 2006), another research lines are open to asses anesthetic depth monitoring in order to analyze the response of the autonomic nervous system (ANS) by the HRV.

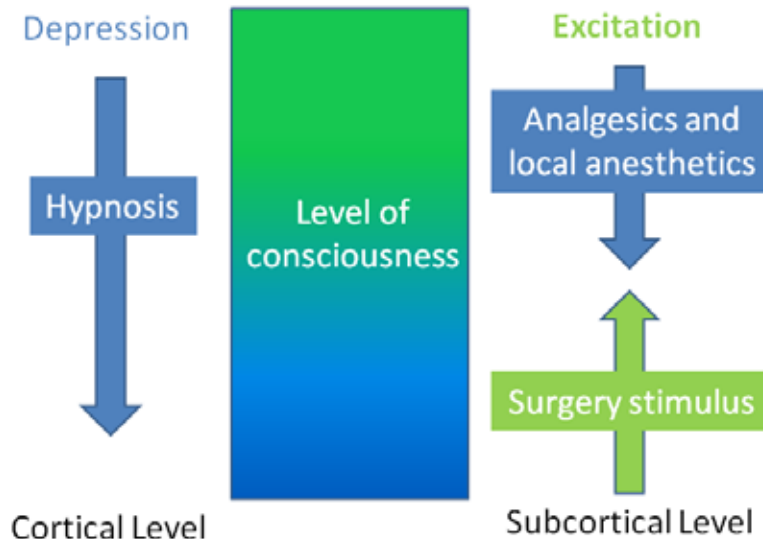


Figure 1.8. General anesthesia: lack of consciousness in the patient

As mentioned above, since the main action of anesthetic agents occurs in the brain, a reasonable choice is to monitor the EEG signal in order to detect changes on its characteristics that are directly related to biochemical variations of a drug induced in the brain. EEG changes (Figure 1.9) and depth of anesthesia in terms of clinical signs are correlated with induction of multidrug anesthesia with propofol and remifentanyl. Both drugs, representing a hypnotic agent and an opioid, respectively, are widely used in the clinical practice and have typical mechanisms of action. The EEG signal is complex in the temporal and spatial level, and, thus, can distinguish brain regions that show changes after administration of a drug. In a work presented by Traast and Kalkman (1995), the power of EEG in different frequency bands was determined and the results indicate pronounced changes in EEG during emergence from propofol/sufentanyl total intravenous anesthesia. Consequently, the EEG signal analysis must become a reliable instrument for determining the activity of a drug, since it assesses the bioavailability of it. Many investigations are based on developing systems for quantification the EEG which try to monitor the hypnotic effect in order to fit the administration of these drugs to the requirements of each patient. This way of facing the problem avoids the problems of under dosing (incidence of intraoperative awakening or consciousness) or overdosing. The BIS[™] (Aspect Medical Systems, Newton, MA) is the first monitor in the marketplace and has become the benchmark comparator for all other monitors. The BIS[™] index, that is a unit-less number between 100 and 0, is a depth of anesthesia (DOA) indicator based on combination of spectral, bispectral and temporal analysis (Rampil, 1998). At present, several EEG based systems for obtaining an indicator of hypnosis are commercially available, being fundamentally different in the method used for signal analysis: the bispectral index (BIS) mentioned above (Rampil, 1998; Billard *et al.*, 1997); the AAI indicator derived from analysis of the signal from auditory evoked potentials (AEP) (Jensen *et al.*, 1996); the indicators derived from the application of entropy to spectral analysis (Vakkuri *et al.*, 2004); the cerebral state index (CSI) obtained from the application of methods of analysis based on fuzzy logic and neural networks (ANFIS) (Verecke *et al.*, 2005); and more recently, the index of consciousness (IoC) and the qCon based on the method of symbolic dynamics. Others studies have used spectral edge frequency (SEF), median frequency and fuzzy soft computation applied to EEG features and total power in the classical frequency bands (Jones *et al.*, 1994; Miller *et al.*, 2005).

However, despite the raised number of different approaches for monitoring depth of anesthesia during surgery, rates are not yet showing a high sensitivity and specificity. In this

way, studies concerning cardiac surgery and obstetrics still have shown higher incidences of 1% of patients with incomplete loss of consciousness during general anesthesia (Gambús *et al.*, 1995; Gambús *et al.*, 2006), which is evidence of traumatic psychological outcome.

Gambús *et al.* (2011) reported important results on the characterization of drug-induced effect hypnotic combining propofol, remifentanyl and opioid analgesic, and the response to stimuli of average aggressiveness (Jensen *et al.*, 2008; Gambús *et al.*, 2011; Borrat *et al.*, 2013) in patients undergoing endoscopic ultrasonography. They studied the characteristics of the pharmacological effect induced by the combination of hypnotic propofol and remifentanyl analgesic, with respect to different effects of hypnotic type (BIS, AAI, IoC, EEG unprocessed, categorical responses) and response to aggressive media stimuli (tube endoscopy introduction) in patients undergoing endoscopy. Their works defined the relationship between the concentration of both drugs and the different effects, establishing the optimum concentration range for the lack of response of the patient.

However, none of the methods discussed above has proven to be clinically useful methods in order to quantify analgesia. The main problems, as discussed previously, include influences of the response of the autonomic nervous system (ANS) and other disturbances, such as changes in blood pressure or heart rate due to patient's baseline condition (hypertension, arrhythmias of diverse etiology), sympathomimetic drug delivery or unpredictable situations such as perioperative bleeding. Some studies indicate that the EEG-based monitors cannot reliably distinguish between light sedation and deep sedation, as these are designed to measure levels of general anesthesia that handles very different levels of hypnosis to those used in sedation procedures. Therefore, still remains the need for a quantitative and objective measurement to quantify the level of sedation in patients undergoing invasive procedures. Additionally, during sedation procedures, patients develop a greater degree of muscular mobility compared to patients undergoing general anesthesia procedures (Chisholm *et al.*, 2006) that may influence the EEG based monitor indexes.

This fact justifies the search of new methods for reliable monitoring of anesthetic depth and sedation. This allows dosing the minimum amount of drug required to prevent intraoperative awareness and/or nociception, while avoiding the drawbacks of excessive dosing.

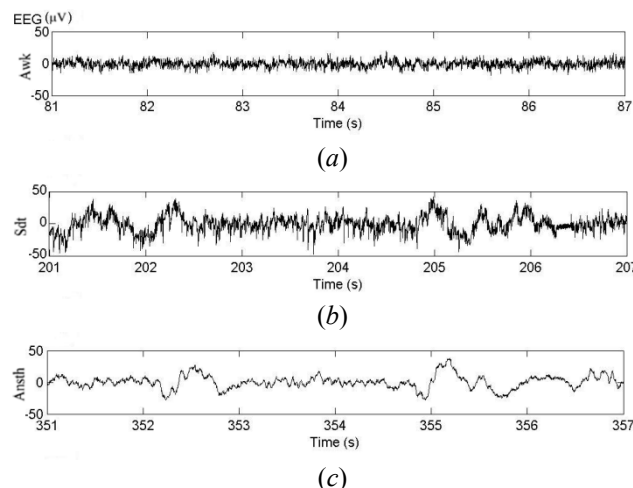


Figure 1.9. Windows of 6 s of unfiltered EEG for each state of DOA: (a) Awk, awake; (b) Sdt, sedated; (c) Ansth, anesthetized

1.5.1 Influence of the individual factors on the anesthesia and sedation level assessment

Several factors have been demonstrated to affect the pharmacokinetics–pharmacodynamics of propofol and remifentanyl. Changes in the pharmacodynamics of anaesthetic agents that occur with increasing age (Schnider *et al.*, 1999), age-related changes in body composition, tissue drug binding and tissue perfusion may affect the distribution, redistribution and elimination of anesthetic agents. These changes may be different between male and female patients (Minto *et al.*, 1997). Vuyk *et al.* (1996) demonstrated that gender affects the pharmacokinetics of propofol in elderly patients resulting in lower concentrations in elderly female patients compared to elderly male patients given the same infusion scheme. Consequently, elderly female patients should be given approximately 10% higher infusion rates compared with elderly male patients to assure that the same blood propofol concentration is reached.

Furthermore, differences in genetic factors might affect the disposition or the sensitivity of the patients to either propofol or remifentanyl. However, the influence of genetic variability in drug dosing of anesthetic drugs has not been widely studied. It is well known that the OPRM1 gene encodes the μ -opioid receptor, which is a member of the G protein-coupled receptor family (Bond *et al.*, 1999). Genetic variations in exon 1 of the OPRM1 gene, located at chromosome 6, have been associated with changes in the spatial conformation of the μ -opioid receptor as a result of amino acid changes in the receptor protein and thereby altering its function. The single nucleotide polymorphism (SNP) of the OPRM1 gene called A118G (rs1799971) results in an amino acid substitution from asparagine to aspartate at mutant receptors (N40D) (Bond *et al.*, 1999; Chou *et al.*, 2007).

Borrat *et al.* (2013) assumed that a genetic trait such as the A118G SNP in the OPRM1 gene can affect the requirements of remifentanyl in patients undergoing procedures under sedation-analgesia. Then, they used it as a covariate factor in the modeling process to optimize dosing of an anesthetic drug. They demonstrated that when an expected decrease in BIS value is not observed after adequate dosing of analgesics, one of the factors to be considered might be the presence of the A118G variant in OPRM gene in chromosome 6. Furthermore, other works have shown that the A118G SNP affects the requirements of opioids to control postoperative pain (Chou *et al.*, 2007) and chronic pain (Klepstad *et al.*, 2004).

1.5.2 Application of nonlinear techniques to EEG signals for the assessment of the anesthesia and sedation level

It is generally known that the EEG signal slows down becoming more regular and less complex as the subject becomes unconscious. Ferenets *et al.* (2006) showed that the various entropy/complexity measures behave in a different manner when related to the clinical assessment of the Ramsay score (a clinical depth of sedation score). He applied five kinds of measures: Shannon entropy (SH), spectral entropy (SpEn), approximate entropy (ApEn), Lempel-Ziv complexity (LZCo), and Higuchi fractal dimension (HFD). While SH increases or remains constant with deepening sedation, the other measures tend to decrease, although, there were exceptions. Huang *et al.* (2003) applied mutual information between four leads for each two-second of the EEG time series.

Although these parameters can distinguish well between awake and anesthetized states, they do not behave monotonically during transition between wakefulness and deep isoelectric states (Miller, 2005). Thus, it is not possible to utilize them individually to continuously monitor anesthetic state changes during different phases of anesthesia and it is essential to utilize an

efficient system to integrate these features. Application of neural networks (NN) in estimating DOA is reviewed by Robert *et al.* (2002). They examined a large number of EEG derived parameters as NN inputs including spectral, entropy, complexity, bicoherence, wavelet transformation derived, autoregressive modeling and hemodynamic parameters as well as a great NN topology such as multilayer perceptron (MLP) and self-organizing networks. Finally, they recommended a two hidden layers MLP model in which their weights are updated after training phase continuously. In a recent work by Lalitha *et al.* (2007), nonlinear chaotic features and neural network classifiers are used to detect anesthetic depth levels. Correlation dimension, Lyapunov exponent (LE) and Hurst exponent (HE) are used as chaotic features and two neural network models are used for classification.

1.6 Thesis aim

According to all the considerations mentioned above, the main focus of this thesis is to evaluate the combination of measures derived from EEG signal recorded during invasive and non-invasive procedures in different states of consciousness, which allow the best assessment of the sedation and analgesia levels by predicting different responses to pain stimulation as well an objective characterization of the ability and the resistance to fall asleep. These indicators would permit a drug control requirements according to the characteristics of each individual, promoting rational use of drugs and helping to improve the results of the surgical process and an automatic detection of the sleepiness, respectively.

In this way, this thesis has the following main objective:

To investigate and implement different methods based on nonlinear techniques in order to develop indexes able to characterize the frequency spectrum, the nonlinear dynamics and the complexity of the EEG signals in different time scales. Then, the purpose is to apply the designed methods to EEG recorded in different states of consciousness for the automatic sleepiness detection, for the analysis of the mismatch component due to nociceptive stimuli and for the prediction of the responses to noxious stimulation during endoscopy procedure. In these studies, it is expected that these new implemented methods will outperform the traditional EEG measures.

For the fulfillment of the main objective of this thesis, the following specific objectives have been proposed:

- Design of the pre-processing method of the EEG signals in order to remove the noise that could influence the analysis.

In order to fulfill this objective, the possible kinds of noise that can affect the EEG signal were evaluated and some procedures of noise-cancellation were selected. This choice was performed following the compromise between the efficiency of the noise-cancellation methods and the possible distortion that the preprocessing procedure can cause to EEG signal. Then, a filter for spike removal based on the analytic signal envelope was designed and tested by analyzing simulated and real EEG signals.

- Implementation and evaluation of nonlinear techniques, including techniques such as time-frequency representations and complexity measures of the time series, which involve information theory techniques as entropies, mutual information functions and correntropy.

To achieve this objective, apart from the respective literature review in order to know the state of the art about the nonlinear techniques applied to EEG signal, it was necessary to implement these techniques so that they could be evaluated on simulated and real EEG data sets. After the literature review, time-frequency representation, Shannon and Rényi entropies, auto-mutual information function and correntropy were considered to fit with the objectives of this thesis. Furthermore, new techniques for calculating the instantaneous spectral entropy and the spectral information entropy were designed. The application of these techniques to simulated time-series allowed them to be evaluated in different conditions such as signals with periodic, random or chaotic behavior. Then, the same techniques were calculated on real EEG databases recorded from a group of healthy and unhealthy patients with different characteristics.

- Evaluation of the nonlinear techniques in the study of the EEG signal for the sleepiness assessment.

To fulfill this objective, all the developed techniques were applied to EEG signals for the assessment of the sleepiness level in patients suffering sleep disorders. A group of patients with excessive daytime sleepiness (EDS) was compared with a group of patients without daytime sleepiness (WDS), by analyzing 60-second EEG windows in waking state. This permitted to evaluate the behavior of the techniques on signals which behavior is already known, in order to validate their capability to characterize the complexity features of the EEG signals. The fulfillment of this goal permitted to know the advantages and disadvantages of these techniques and to find which measures obtained with these techniques could characterize the complexity and the nonlinear behavior of the EEG signals, yielding higher statistical significance than the traditional measures.

- Application of the selected measures to EEG signals for analyzing event related potentials (ERP) due to different type of nociceptive stimulations.

This study focused on the optimization in the analysis of the mismatch negativity (MMN) component due to frequent and infrequent stimuli under thermal and electric stimulation. Two kinds of stimulation were studied in order to optimize the description of the response to the stimulus. The main objectives were to differentiate the ERP from the noise due to normal brain activity and to characterize the responses to infrequent and frequent stimulation in healthy subjects in order to describe the processes involved in the generation of the MMN. It was of interest to study how adaptation and fatigue affect the ERP due to stimuli of different modalities.

- Application of the selected measures on signals recorded from patients undergoing endoscopy in order to predict the responses to pain stimulation during sedation.

To achieve this goal, the selected measures were applied to EEG filtered in the traditional bands and in higher frequency bands. It was assumed that taking into account also the frequency bands where scalp and facial muscle EMG components are present, the prediction of the responses to pain stimulation during endoscopy procedure can be improved. In this sense, it might be possible to associate an increased activity in the facial muscles with a greater possibility of pain, obtaining a better prediction of responsive states. Univariate and multivariate discriminant analysis was applied to select the measures that showed significant differences in the prediction of no-response, sluggish responses and stronger responses to nail bad compression corresponding to different sedation levels. Finally, the proposed variables that gave the highest statistical performances were used in the prediction of the gag reflex during endoscopy tube insertion, in order to evaluate their behavior in the prediction of the response to a different type of stimulus.

The achievement of these goals gave the possibility to select from a set that includes clinical indices, time-frequency domain and nonlinear techniques, those measures that improved

the non-invasive prediction of pain responses during sedation. Likewise, it is expected that the proposed measures can be useful for improving the existent indexes for the assessment of the sedation level.

Chapter 2

Database

This chapter contains the description of the databases used throughout the entire doctoral thesis. Section 2.1 presents two databases built with simulated signals that were used for evaluating the preprocessing and the time-frequency and non-linear methods. Section 2.2 describes the four databases that contain experimental EEG data recorded from healthy subjects or patients suffering different disorders. Two of the EEG databases were used in order to test the proposed methods based on time-frequency representation and non-linear techniques. The other two EEG databases were used in order to calculate the EEG measures based on time-frequency representation and non-linear techniques for the characterization and the prediction of nociceptive responses.

2.1 Synthetic signals

Two databases of synthetic signals were developed in order to simulate different situation of EEG signal and noise as well different EEG behaviors. The first one, containing simulated EEG signal corrupted by peak and spike noise, was used for evaluating the designed algorithm (ASEF) for peak and spike removal. The other one, containing signals with different periodicity and complexity behavior, was used for evaluating the proposed methods for calculating the instantaneous entropy and spectral information entropy based on time-frequency representation.

2.1.1 Noisy signals

A set of simulated time series $x(t)$ of EEG signals corrupted by peak or spike noise was generated.

$$x(t) = s(t) + n(t) \quad (2.1)$$

where $s(t)$ represents the pure EEG signal and $n(t)$ represents a signal containing random events of peak or spike waveforms.

The signals $s(t)$ were created by using functions that generate simulated EEG data (Yeung *et al.*, 2004). These functions create uncorrelated noise generated such that its power spectrum matches the power spectrum of human EEG. The simulated EEG was constructed by summing together a number of phase-randomized sinusoids (frequencies from 0.1 to 125 Hz and phases between 0 and 2π), the amplitude of which varied with frequency according to the power spectrum of empirical EEG data. Because this process amounts to an inverse-Fourier transform (with randomized phase) of a spectral analysis of real data, the simulated data match closely the features of empirically observed EEG data (Yeung *et al.*, 2007). The mean value of $s(t)$ is $\overline{s(t)} = 0$ and the standard deviation is bounded $0.6 < \sigma_s < 1 \mu\text{V}$.

The noise $n(t)$ was created combining peak and spike events with random amplitude and random frequency of occurrence, in order to simulate the worst noisy case in the EEG signal. The spike events were simulated with triangle waveforms, $tri(t)$

$$tri(t) = \begin{cases} \mu_{tri}(1 - |t - t_{tri}|): & \text{if } 0 \leq t \leq 2t_{tri} \\ 0: & \text{otherwise} \end{cases} \quad (2.2)$$

where μ_{tri} is a random variable that has normal distribution with expected value $\bar{\mu}_{tri} = 0$, standard deviation $20\sigma_s$, and $t_{tri} = 0.04$ s. These values permitted to create triangle waveforms with negative or positive values about 20 times the maximum EEG value and with duration that simulates short-time spike EEG artifacts. Then, the signal noise $n(t)$ was built as

$$n(t) = \begin{cases} tri(t - t_{n1}): & \text{if } t = t_{n1} \\ \mu_{peak}: & \text{if } t = t_{n2} \\ 0: & \text{otherwise} \end{cases} \quad (2.3)$$

where μ_{peak} is a random variable that has normal distribution with expected value $\bar{\mu}_{peak} = 0$ and standard deviation $20\sigma_s$, $t_{n1} \in T_1 = \{t_{11}, t_{21}, t_{31}, \dots, t_{N1}\}$ and $t_{n2} \in T_2 = \{t_{12}, t_{22}, t_{32}, \dots, t_{N2}\}$, $\forall n = 1, 2, \dots, N$ with $N = 40$. Where t_{n1} and t_{n2} are random variables with normal distribution and expected value $\bar{t}_{n1} = 50$ s and standard deviation $\sigma_m = 50$ s. These values permitted to create noise events, with negative or positive values about 20 times the maximum EEG value, that occur between 0 s to 100 s with Gaussian distribution.

Two sets of 1000 signals $x(t)$ were generated with a sampling frequency of 256 Hz and a length of 100 s: set EEG1, 1000 signals corrupted with isolated peak and spike noise; set EEG2, 1000 signals corrupted with isolated peak and spike noise and with 20 consecutive triangle waveforms ($tri(t)$) in two randomly selected windows of 2 s along the signal. In this way, set EEG2 contains signals more contaminated than EEG1. Figure 2.1 shows an example of a simulated signal from EEG2 set.

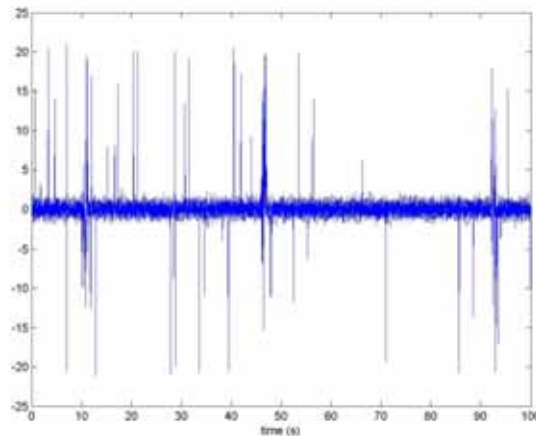


Figure 2.1. EEG2 set: simulated EEG signal with peak and spike noise

2.1.2 Periodic, random and chaotic signals

In order to study the performances of the instantaneous entropy and spectral information entropy a set of different simulated signals were designed:

1. A periodic signal (signal 1) $x(t) = \sum A_s \sin(2\pi F_i t)$ was generated adding a frequency component (F_i) every 25 s, in this way the first 25 s segment of the signal has 1 frequency component and the last 25 s segment has 8 frequency components. The added frequencies were respectively $F_i = [0.5; 1; 2; 5; 10; 20; 30; 50]$ Hz. The amplitude of each frequency component was $A_s = 1$. Figure 2.2 shows an example of signal 1.
2. A MIX process (signal 2), used in previous studies (Pincus, 1991; Ferrario *et al.*, 2006; Escudero *et al.*, 2009), was defined as $MIX = (1 - z)x + zy$, where z is a random variable that is equal to 1 with probability p and equal to 0 with probability $1-p$, x is a periodic sequence with a frequency component of 10 Hz, and y is a standard uniformly distributed variable on $[-\sqrt{3}, \sqrt{3}]$. The synthetic signal 2 was based on a MIX process whose parameter p varied linearly from 0.9 to 0.1. Hence, this sequence, evolved from randomness to periodicity. Figure 2.3 shows an example of signal 2.
3. Signal 3 was built with the same MIX process of signal 2 using as y the Hx obtained from Henon map (Davies, 1999) with a chaotic behavior described in (2.4), using the canonic values $a = 1.4$ and $b = 0.3$, and taking $Hx(0) = 0.5$ and $Hy(0) = 0.5$ as initial conditions. Hence, this sequence evolved from chaos to periodicity. Figure 2.4 shows an example of signal 3.

$$\begin{cases} Hx(n + 1) = 1 - a Hx^2(n) + Hy(n) \\ Hy(n + 1) = b Hx(n) \end{cases} \quad (2.4)$$

4. Signal 4 was built with the same MIX process of signal 3 using as y a Henon map with chaotic behavior and as x the standard uniformly distributed variable on $[-\sqrt{3}, \sqrt{3}]$. Hence, this sequence evolved from chaos to randomness. Figure 2.5 shows an example of signal 4.

All synthetic signals had a length of 200 s and a sampling frequency of 128 Hz.

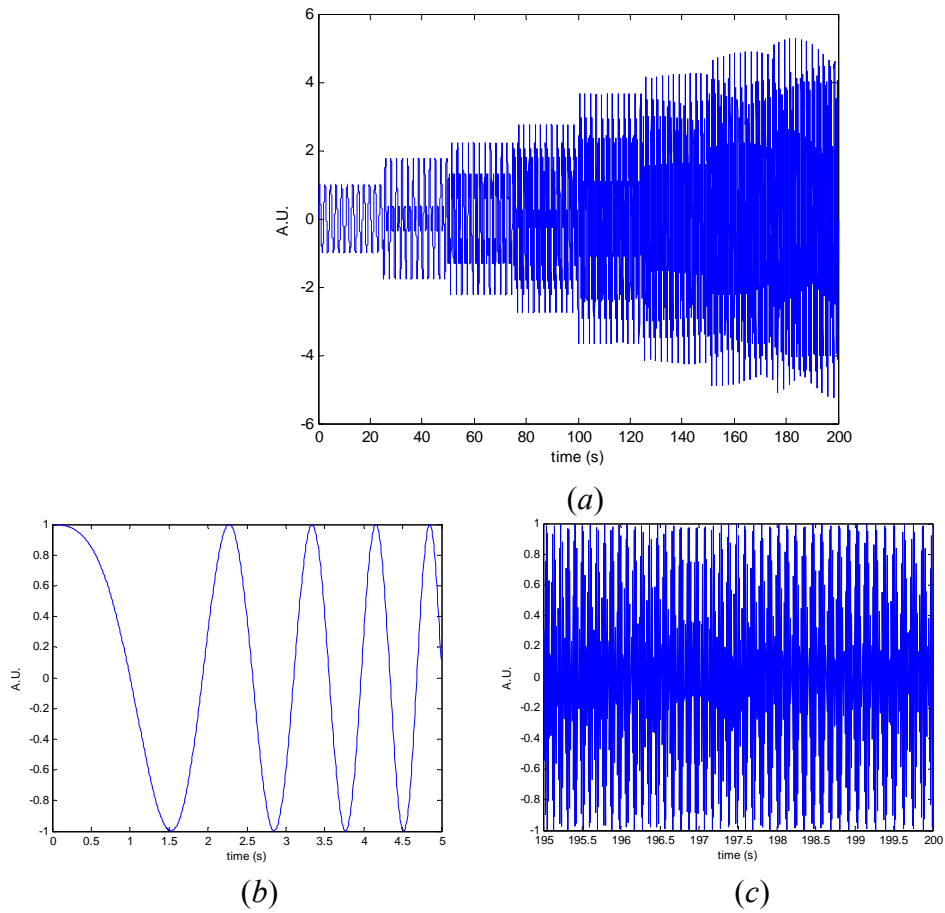
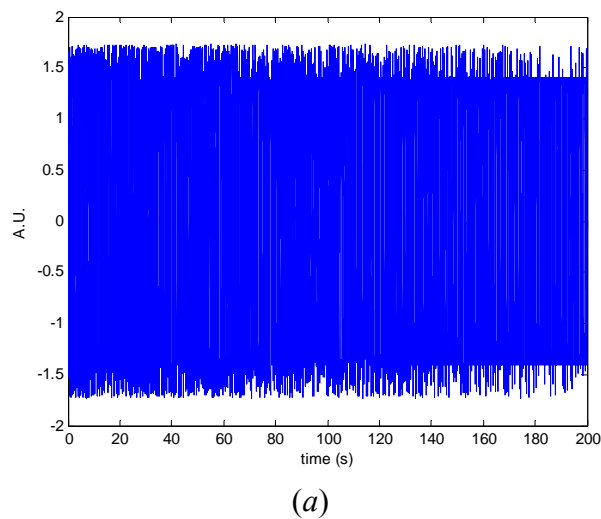


Figure 2.2. (a) Evolution of the periodic signal 1; (b) the first 5 s of signal 1 where only one frequency component is present ($F_1=0.5$ Hz); (c) the last 5 s of signal 1 where all the frequency components are present ($F_i = [0.5; 1; 2; 5; 10; 20; 30; 50]$ Hz)



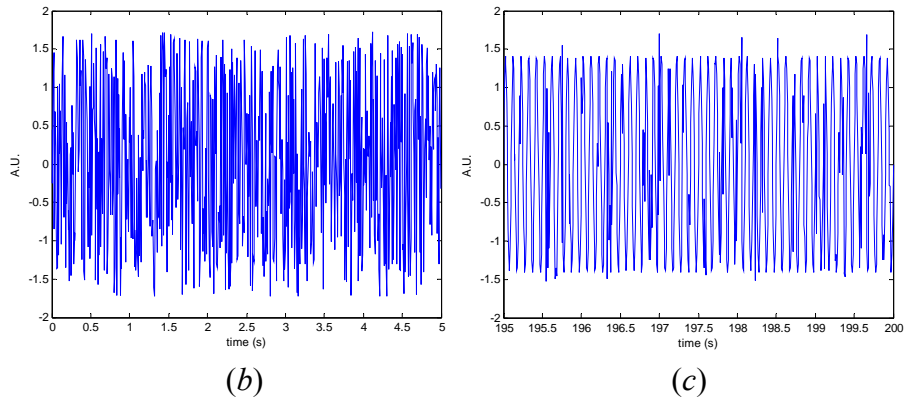


Figure 2.3. (a) Evolution of signal 2; (b) the first 5 s of signal 2 characterized by a more random behavior; (c) the last 5 s of signal 2 characterized by a more periodic behavior

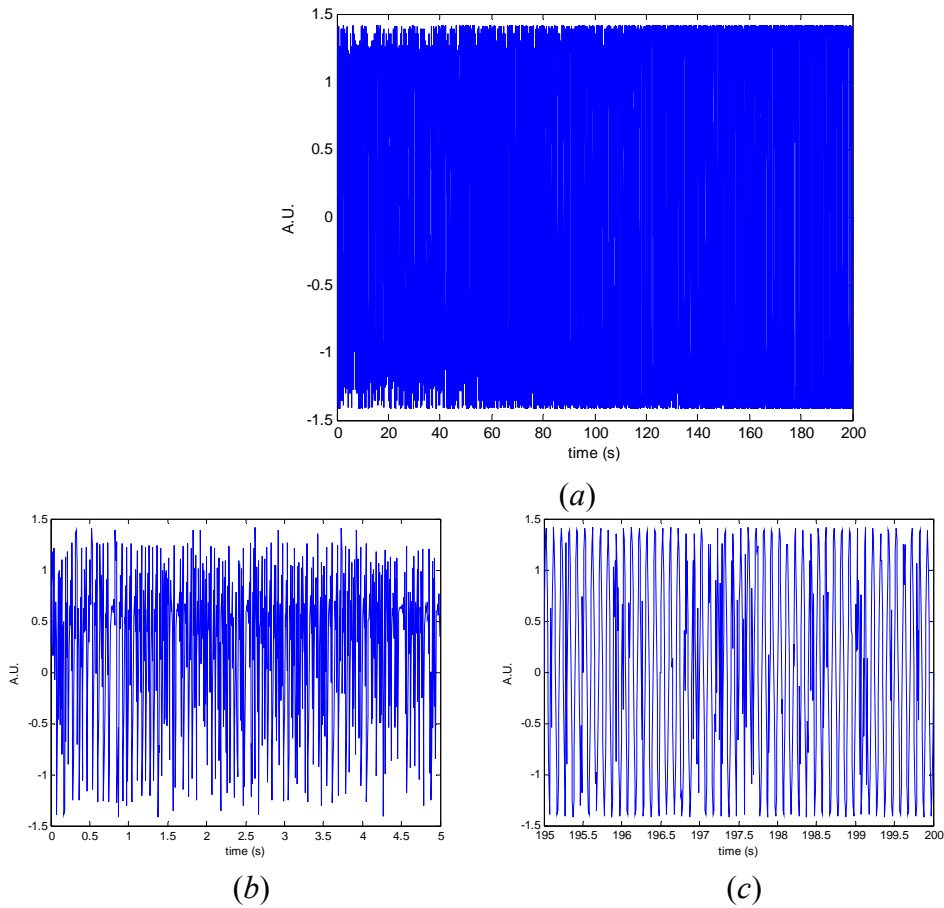


Figure 2.4. (a) Evolution of signal 3; (b) the first 5 s of signal 3 characterized by a more chaotic behavior; (c) the last 5 s of signal 3 characterized by a more periodic behavior

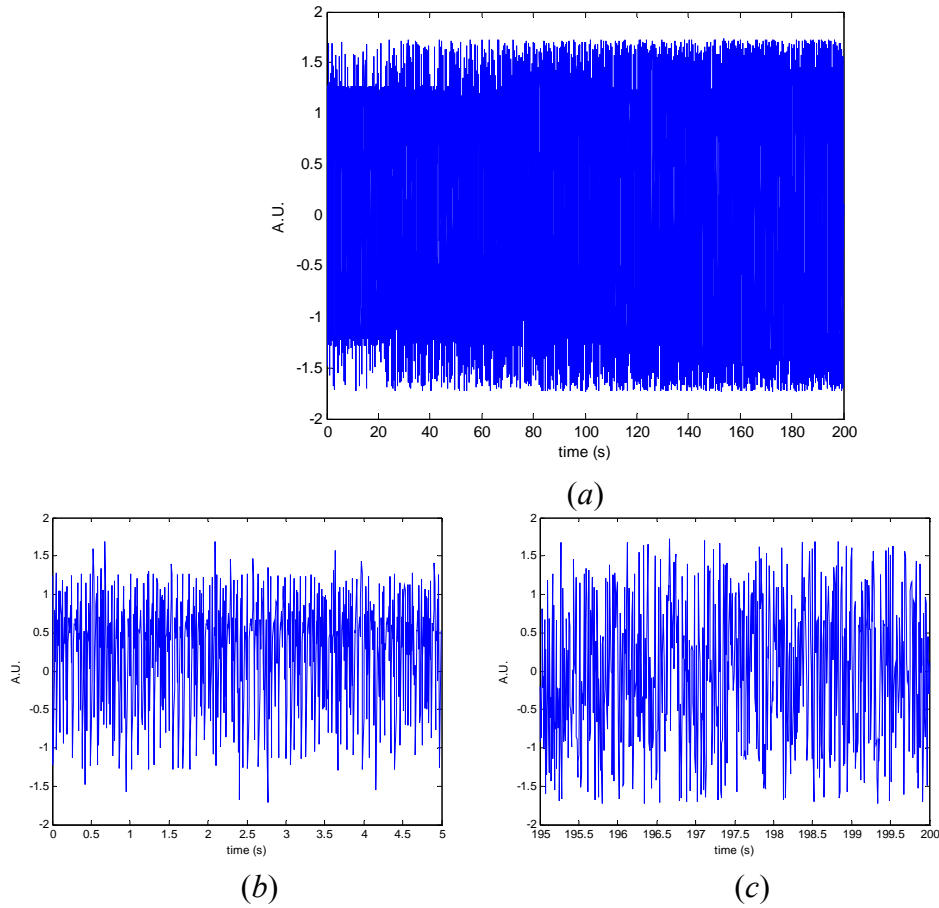


Figure 2.5. (a) Evolution of signal 4; (b) the first 5 s of signal 4 characterized by a more chaotic behavior; (c) the last 5 s of signal 4 characterized by a more random behavior

2.2 Real EEG signals

The developed methods were applied to four databases that contain experimental EEG data recorded from healthy subjects and patients suffering different disorders. These real EEG databases were classified in two subgroups, in order to accomplish two different aims: 1) to evaluate the proposed methods by using two real EEG databases with known behavior; 2) to validate the capability of the proposed EEG measures to characterize and predict the nociceptive responses, by using two real EEG databases.

2.2.1 EEG signals for evaluating the methods

One database, containing EEG signals recorded in different states (eyes-open or eyes-closed, ictal and non-ictal activity) from healthy subjects and patient suffering epilepsy, was used to test the ASEF algorithm and the instantaneous entropy and spectral information entropy. The other database, containing EEG signals recorded from patients suffering sleep disturbances that underwent the maintenance of wakefulness test (MWT) and multiple sleep latency test (MSLT), was used to test the proposed methods for the automatic detection of sleepiness.

2.2.1.1 “ABCDE” database

This is a freely available EEG dataset (Andrzejak *et al.*, 2001) that contains 100 single channel EEG segments of 23.6 s, recorded with the same amplifier system. An average common reference was used and the sampling rate was fixed to 173.6 Hz. The dataset was divided in five different sets (A, B, C, D, E). Sets A and B contain surface EEG signals recorded from five healthy volunteers who were relaxed in an awake state. Whereas the subjects had their eyes open during the recording of the EEG in set A, the EEG signals of dataset B were acquired with eyes closed. Three sets (C, D and E) of intracranial EEG were recorded from five epileptic patients, who had achieved complete seizure control after a surgical procedure. Signals in set D were recorded within the epileptogenic zone, whereas the EEG signals of set C were acquired from the opposite brain hemisphere. Sets C and D contained only activity measured during seizure-free intervals. On the other hand, set E was only composed of seizure activity recorded from all sites exhibiting ictal activity. Additional details can be found in (Andrzejak *et al.*, 2001).

2.2.1.2 MWT-MSLT database

This database belongs to the Multidisciplinary Sleep Disorders Unit of the Hospital Clínic (Barcelona, Spain). From a series of 98 consecutive patients with symptoms of sleep disorder breathing (SDB), 2 groups of 20 patients were selected consecutively based on a MWT-MSLT research protocol: excessive daytime sleepiness (EDS) group (MWT < 20 min and MSLT < 8 min) and without daytime sleepiness (WDS) group (MWT > 20 min and MSLT > 8 min). Patients were matched by age and gender. For each patient, 6 channels of EEG (F3,F4,C3,C4,O1,O2) referenced to linked earlobes (A1+A2)/2 were recorded at 256 Hz during the test MWT and MSLT. The MSLT and MWT consisted of a series of five nap opportunities during the day beginning approximately one hour after morning awakening, starting with the MWT and alternating each other throughout the day. The MSLT is performed with the subject lying down in bed in a comfortable position in a dark and quiet room with explicit instruction to try to fall asleep, while the MWT with subjects semi-recumbent in a bed and with the instruction to stay awake. If no sleep occurred, MWT and MSLT trials were ended after 40 and 20 minutes respectively, or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep. Objective daytime sleepiness was measured from sleep latency defined as time from lights out to the first epoch of unequivocal sleep on each test (Richardson *et al.*, 1978; Carskadon *et al.*, 1986; Thorpy *et al.*, 1992). The study received approval from the Ethics Committee of Hospital Clinic de Barcelona.

After the application of a FIR band pass filter of 50th order, with cut-off frequencies of 0.1-45Hz, the EEG channels were resampled at 128 Hz. Then, the EEG was segmented in 60 s sliding windows with step of 20 s calculated during the entire tests. The raw EEG was visually checked in order to avoid the analysis of EEG windows corrupted by strong artifacts. In general, the first 30 s of each MWT and MSLT trials were not taken into account because they were altered by movement artifacts due to patients trying to find their comfortable position. Furthermore, windows that contain high amplitude ocular artifacts were rejected and the subsequent windows were taken into account for the analysis. The selected windows were filtered into the characteristic frequency bands of the EEG signal: δ , 0.1-4 Hz; θ , 4-8 Hz; α , 8-12 Hz; β , 12-30 Hz; total band TB , 0.1-45 Hz.

2.2.2 EEG signal for the characterization and the prediction of nociceptive responses

One database was recorded in healthy subjects who underwent the application of thermal, electric and auditory stimulation. The other database was recorded in patients undergoing ultrasonographic endoscopy of the upper gastrointestinal tract under sedation and analgesia with propofol and remifentanyl.

2.2.2.1 ERP-MMN database

This database belongs to the Neurology Department of the Hospital Clínic (Barcelona, Spain). Three types of stimuli were applied to each subject following established recommendations: thermal (Greffrath *et al.*, 2007), electric (Restuccia *et al.*, 2007) and auditory (Näätänen and Alho, 1995). For contact heat stimuli, a pair of thermofoil thermode stimulators were used, each with a surface area of 572.5 mm² (Pathway, Medoc Ltd, Ramat Yishai, Israel), set to reach a temperature of 53°C at a rate of 70°C/s. The thermodes were attached to the dorsum of the hand side by side. Electromyograph (KeypointNED, Alpine) was used for electrical stimuli, and set at an intensity of 8mA. The electrical stimuli were applied with surface electrodes to the second and fourth finger of the right hand. The auditory stimuli were delivered through a pair of headphones (right and left).

EEG was recorded from 25 healthy subjects (11 males and 14 females), aged 22 to 54 years. The study received approval from the Ethics Committee of Hospital Clinic de Barcelona. Subjects were reading a book to divert their attention from the stimulus. The percentage of random infrequent (*I*) and frequent (*F*) stimuli over full rate was 20% and 80%, respectively. All ERPs were recorded from three EEG channels (Cz, C3 and C4) referenced to linked earlobes (A1-A2). All recordings were carried out with a V-Amp (BrainVision) at a sampling rate of 1000 Hz. The impedance was kept below 5 kΩ.

For the test on thermoalgesic stimuli, a total of 400 stimuli through one thermode (*F*) and 100 through the other (*I*) were applied, switching also between thermodes at 200/50. A total of 800 electrical stimuli (*F*) to one finger and 200 stimuli to the other finger (*I*) were applied, switching fingers at 400/100. For the auditory study, a total of 800 tones at 1000 Hz (*F*) and 200 tones at frequency of 1100 Hz (*I*) were applied. In this way, *I* stimulus occurs approximately each 4 or 5 *F* stimuli. The stimulation rate was 0.6 Hz for thermal stimulation, and 0.9 Hz for electrical and auditory stimulation. The mean total recording time for each subject (including auditory, electrical and thermal stimulus) was about 45 minutes.

EEGs were filtered with a Butterworth band-pass filter of 5-th order with cut-off frequencies of 0.1-45Hz in order to reduce the influences of the EMG, EOG and the external noise. Then, they were down sampled to 125 Hz with a FIR decimation filter of 30-th order. Finally, EEGs were segmented in windows taken from 0 s to 1 s after each stimulus. The first 50 windows (*Start*) and the last 50 windows (*End*) were respectively averaged, in order to be analyzed. The windows of *F* stimulation response subsequent to an *I* stimulation were not taken into account in the present study. This study was applied to the Cz scalp recordings since the vertex potential is indeed the largest and best defined of all recording scalp sites to nociceptive stimuli (Casanova *et al.*, 2011).

2.2.2.2 Anesthesia and sedation database

The database belongs to the Department of Anesthesiology, Hospital Clínic of Barcelona (Spain). This database contains data recorded from 378 patients (247 men, mean age 63±23

years) undergoing ultrasonographic endoscopy of the upper gastrointestinal tract under sedation and analgesia with propofol and remifentanyl. Figure 2.6 shows the distribution of the ages of the male and female patients. All the patients belong to 1-3 ASA classification. Patients with altered central nervous system, medicated with analgesics or drugs with central effects on the perception of pain, from moderate to severe cardiomyopathy, neuropathy or hepatopathy that needed control during the anesthetic process were not included in the database. The study received approval from the Ethics Committee of Hospital Clinic de Barcelona and all the patients signed informed consent. For each patient, the following information is available: predicted concentrations of propofol (C_{eProp}) and remifentanyl (C_{eRemi}); bispectral Index (BIS) and electroencephalogram (EEG) signal. The observed categorical responses after applied nociceptive stimuli include the evaluation of the RSS (see Table 2.1) (Ramsay *et al.*, 1974) after nail bed compression and the presence of gag reflex during endoscopy tube insertion (GAG). Specifically, RSS 2, 3, 4 and 5 correspond to patients who respond with purposeful movement after nail bed compression while patients in the RSS 6 category do not respond. GAG corresponds to a positive nausea reflex during endoscopy tube insertion, a noxious stimulus as well. The RSS score was evaluated at random times during the procedure to avoid those factors correlated with time, which could confound the results of the RSS measurements. The whole database contains annotated RSS scores from 2 to 6.

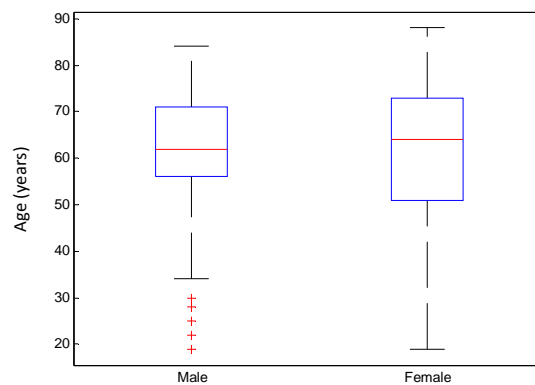


Figure 2.6. Distribution of the ages of the patients. On each box, the central mark is the median; the edges of the box are the 25th and 75th percentiles. The whiskers are lines extending from each end of the boxes to show the extent of the rest of the data. Values beyond the end of the whiskers are considered outliers and marked with a +

Table 2.1. Ramsay sedation scale.

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

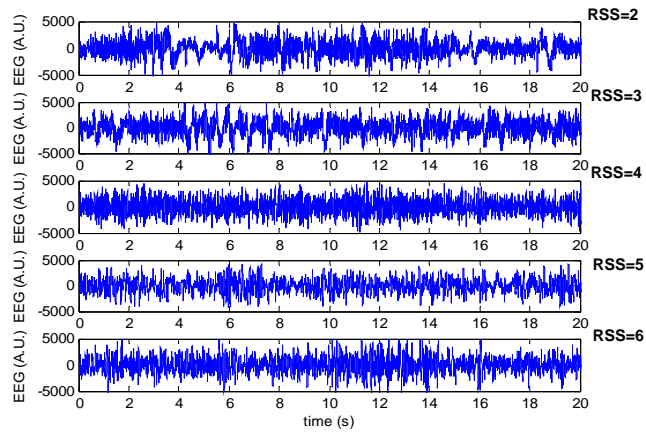
The EEG was recorded with a sampling frequency of 900 Hz, with a resolution of 16 bits and a recording time of about 60 min using AEP monitor/2 (Danmeter, Odense, Denmark). A 3-electrode montage was used: middle forehead (+), malar bone (-), and left forehead electrode used as reference. Propofol and remifentanyl were infused using a TCI system (FreseniusVial;

Chemin de Fer, Béziers, France). All information Ce_{Prop} , Ce_{Remi} , BIS, RSS and GAG were annotated with a resolution of 1 s.

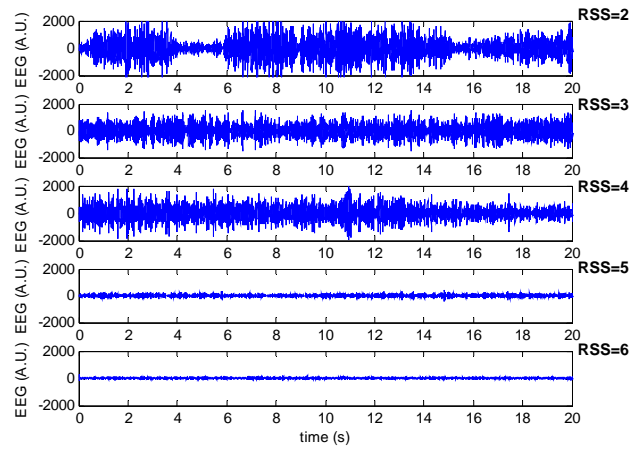
The analysis in the traditional band was performed on EEG signals filtered between 0.1-45 Hz and resampled at 128 Hz while high frequency analysis were performed on EEG filtered between 0.1-145 Hz and resampled at 300 Hz. After the resampling process, the EEG signals were segmented in windows of length of 1 minute between 30 s and 90 s before the response annotation of RSS or GAG, in order to avoid the effect of the stimulation on the signal. The selected windows were filtered into the following frequency bands: δ , 0.1-4 Hz; θ , 4-8 Hz; α , 8-12 Hz; β , 12-30 Hz; HF ; 60-95 Hz and VHF ; 105-145 Hz; TB , 0.1-145 Hz. Figure 2.7 shows an example of 20 second-windows of EEG filtered in TB , HF and VHF bands for different RSS scores.

The annotated RSS was assigned to the previous 1 minute length window if the differences ΔCe_{Remi} and ΔCe_{Prop} between the first and the last second of the window were $\Delta Ce_{Remi} < 0.1$ ng/ml and $\Delta Ce_{Prop} < 0.1$ μ g/ml. Otherwise, the window was taken till the sample where the conditions were satisfied.

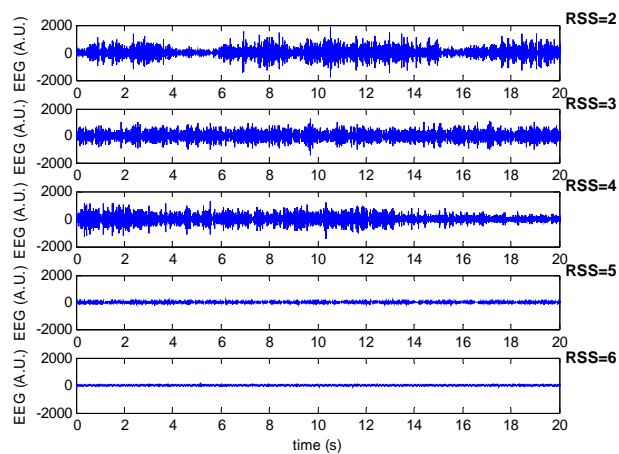
For a subset of patients (OP01) the information about the presence (OP=1) or absence (OP=0) of the single nucleotide polymorphism (SNP) A118G in gene OPRM1 is provided. Before starting the endoscopic procedure, a venous blood sample was drawn from every patient for posterior genetic analysis to detect A118G SNP. Genomic DNA was isolated from blood using the QiaAmp® DNA Mini kit (Qiagen, Courtaboeuf, France) according to the manufacturer's instructions. Genotyping for A118G SNP was performed by TaqMan® (Invitrogen, Life Technologies Ltd., Paisley, United Kingdom) and allelic discrimination by using a predesigned SNP Genotyping Assay in the 7300 Real-Time PCR System (Applied Biosystems, Foster City, CA) following the manufacturer's instructions. Genotyping was scored manually and blindly by two independent operators to avoid errors.



(a)



(b)



(c)

Figure 2.7. EEG windows filtered in (a) TB, (b) HF and (c) VHF bands associated with different RSS scores

Chapter 3

Results

This chapter presents the results of this thesis that are contained in seven publications. After the description of the framework of the thesis and a summary of the main results, the publications are listed and grouped by their respective topics.

3.1 Framework of the thesis

This doctoral thesis is framed in the research project “Signal processing and bioinformatics tools for multilevel assessment of cardiovascular disorders and anesthesia monitoring: phenotypic approach” (MICINN TEC 2010-20866-C02-01, 2010-2013 extended from 2013 to 2014) in the Departament d’Enginyeria de Sistemes, Automàtica i Informàtica Industrial (ESAI) and the Centre de Recerca en Enginyeria Biomèdica (CREB) at the Universitat Politècnica de Catalunya – BarcelonaTech (UPC) in collaboration with Hospital Clinic (Barcelona) and Quantum Medical (Mataró).

3.2 Summary of the results

This thesis was under the scope of biomedical signal processing and analysis. Its main objective was to investigate and implement different methods based on nonlinear techniques in order to develop indexes able to characterize the frequency spectrum, the nonlinear dynamics and complexity of the EEG signals. The results obtained during the different studies, which were carried out in the thesis development, are collected in seven papers. Five of them are already published in scientific journal indexed in the journal citation report (JCR), while the other two are submitted in scientific journal indexed in JCR but they are still in the review process.

The first listed paper, published in the journal “Medical, Engineering & Physics”, presents a new methodology to reduce peak and spike artifacts based on the analytic signal envelope. This method can be applied to EEG single-channel recording without using any reference signal. The values of the parameters that optimize the algorithm performances are calculated and reported. The algorithm was tested on simulated and real EEG signals that contain peak and spike artifacts with random amplitude and frequency occurrence. The performance of the filter was compared with commonly used adaptive filters. It was found that the new proposed filter was able to reduce the amplitude of peak and spike artifacts with performances significantly better than the traditional adaptive filters. Three indexes were used for testing the performance of the filters: Correlation coefficient (ρ), mean of coherence function (C) and rate of absolute error (RAE). All these indexes were calculated between filtered signal and original signal without noise. It was found that the new proposed filter was able to reduce the amplitude of peak and spike artifacts with $\rho > 0.85$, $C > 0.8$, $RAE < 0.5$. These values were significantly better than the performance of LMS adaptive filter ($\rho < 0.85$, $C < 0.6$, and $RAE > 1$). This algorithm was used in the works of this thesis when the EEG presented peak and spike noise.

In the paper published in the journal “Entropy”, the theory of Shannon entropy was applied to the Choi-Williams time-frequency distribution (CWD) of time series in order to extract entropy information in both time and frequency domains. Four novel indexes were defined by calculating entropy of the CWD with respect to time or frequency, by using the probability mass function at each time instant taken independently or by using the probability mass function of the entire CWD. These indexes were tested on synthetic time series with different behavior (periodic, chaotic and random) and on a dataset of EEG signals recorded in different states (eyes-open, eyes-closed, ictal and non-ictal activity). The results have shown that the values of these indexes tend to decrease, with different proportion, when the behavior of the synthetic signals evolved from chaos or randomness to periodicity. Statistical differences (p -value <0.0005) were found between values of these measures comparing eyes-open and eyes-closed states and between ictal and non-ictal states in different EEG frequency bands. In this way, this paper has demonstrated that the proposed measures can be useful tools to quantify the different periodic, chaotic and random components in EEG signals.

The third and the fourth paper are published in the journals “Journal of Medical and Biological Engineering” and “Physiological Measurement”, respectively, while the fifth paper is submitted in the journal “Medical, Engineering & Physics” currently under major revision. In these papers, measures obtained with time-frequency representation, correntropy, auto-mutual information function (AMIF) and cross-mutual information function (CMIF) were applied to EEG signals for the assessment of the level of sleepiness in patients suffering sleep disorders. A group of 20 patients with excessive daytime sleepiness (EDS) was compared with a group of 20 patients without daytime sleepiness (WDS), by analyzing 60-second EEG windows in waking state. Statistical differences (p -value <0.005) between EDS and WDS groups were found in δ and θ frequency bands using CWD. The results showed that the EDS group presented more power in θ band than WDS, while WDS group presented higher spectral and cross-spectral entropy than EDS in the frontal zone in δ band. Measures based on correntropy, cross-correntropy, AMIF and CMIF permitted the quantification of complex signal properties and the non-linear couplings between different areas of the scalp. Statistical differences (p -value <0.0001) between EDS and WDS groups were mainly found in the β band. The WDS group presented more complexity in the occipital zone than the EDS group, while a stronger nonlinear coupling between the occipital and frontal regions was detected in EDS patients than in the WDS group. Measures based on mutual information (AMIF and CMIF) and correntropy yielded sensitivity and specificity above 80% and area under ROC curve (AUC) above 0.85 in classifying EDS and WDS patients. The statistical performances of the AMIF, CMIF and correntropy measures represent an improvement compared to classical EEG indices and to time-frequency indexes applied in the same database.

In the sixth paper, time-frequency representation and nonlinear measures as spectral entropy and AMIF were applied to EEG in order to study how adaptation and fatigue affect the event-related brain potentials to stimuli of different modalities. The responses to infrequent and frequent stimulation in different recording periods were characterized in series of averaged EEG epochs recorded after thermal, electrical and auditory stimulation. The statistical analysis evidenced differences in windows of response to infrequent and frequent stimuli between the start and end of the EEG recording, permitting to observe some aspects of the subject adaptation and the nociceptive response. The defined measures presented a statistical significance p -value <0.01 and accuracy higher than 60% by differentiating windows of response to infrequent and frequent stimuli between the start and end of the EEG recording.

A seventh paper (under review) proposes a set of EEG measures that improved the assessment of the level of sedation. These measures were obtained by applying all the developed techniques on signals recorded from patients undergoing endoscopy, in order to predict the

responses to pain stimulation during sedation. Discriminant analysis between EEG recorded before nail bad compression and tube insertion were performed in order to classify between different pain responses. The proposed measures exhibit better performances than the bispectral index (BIS). Values of prediction probability of Pk above 0.75 and percentages of sensitivity and specificity above 70% were achieved combining EEG measures from the traditional frequency bands and higher frequency bands.

3.3 Publication collection

The following sections present the publications that contain the results of this doctoral thesis. All the publications are grouped by topics and ordered to follow the path formed by the thesis objectives. As mentioned above, further than the published papers contained in the official publication collections of this thesis, other two submitted paper that are in the revision process are presented in the following sections as a part of this doctoral thesis.

3.3.1 Filtering and thresholding the analytic signal envelope in order to improve peak and spike noise reduction in EEG signals

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Technical note, Technical Note

Filtering and thresholding the analytic signal envelope in order to improve peak and spike noise reduction in EEG signals



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ABSTRACT

To remove peak and spike artifacts in biological time series has represented a hard challenge in the last decades. Several methods have been implemented mainly based on adaptive filtering in order to solve this problem. This work presents an algorithm for removing peak and spike artifacts based on a threshold built on the analytic signal envelope. The algorithm was tested on simulated and real EEG signals that contain peak and spike artifacts with random amplitude and frequency occurrence. The performance of the filter was compared with commonly used adaptive filters. Three indexes were used for testing the performance of the filters: Correlation coefficient (ρ), mean of coherence function (C), and rate of absolute error (RAE). All these indexes were calculated between filtered signal and original signal without noise. It was found that the new proposed filter was able to reduce the amplitude of peak and spike artifacts with $\rho > 0.85$, $C > 0.8$, and $RAE < 0.5$. These values were significantly better than the performance of LMS adaptive filter ($\rho < 0.85$, $C < 0.6$, and $RAE > 1$).

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3.3.2 Measuring instantaneous and spectral information entropies by shannon entropy of Choi-Williams distribution in the context of electroencephalography

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Article

Measuring Instantaneous and Spectral Information Entropies by Shannon Entropy of Choi-Williams Distribution in the Context of Electroencephalography

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Abstract: The theory of Shannon entropy was applied to the Choi-Williams time-frequency distribution (CWD) of time series in order to extract entropy information in both time and frequency domains. In this way, four novel indexes were defined: (1) partial instantaneous entropy, calculated as the entropy of the CWD with respect to time by using the probability mass function at each time instant taken independently; (2) partial spectral information entropy, calculated as the entropy of the CWD with respect to frequency by using the probability mass function of each frequency value taken independently; (3) complete instantaneous entropy, calculated as the entropy of the CWD with respect to time by using the probability mass function of the entire CWD; (4) complete spectral information entropy, calculated as the entropy of the CWD with respect to frequency by using the probability mass function of the entire CWD. These indexes were tested on synthetic time series with different behavior (periodic, chaotic and random) and on a dataset of electroencephalographic (EEG) signals recorded in different states (eyes-open, eyes-closed, ictal and non-ictal activity). The results have shown that the values of these indexes tend to decrease, with different proportion, when the behavior of the synthetic signals evolved from chaos or randomness to periodicity. Statistical differences (p -value < 0.0005) were found between values of these measures comparing eyes-open and eyes-closed states and between ictal and non-ictal states in the traditional EEG frequency bands. Finally, this paper has demonstrated

Entropy **2014**, *16*

2531

that the proposed measures can be useful tools to quantify the different periodic, chaotic and random components in EEG signals.

Keywords: entropy; time-frequency representation; electroencephalography; complexity

3.3.3 Characterization of daytime sleepiness by time-frequency measures of EEG Signals

1

Characterization of Daytime Sleepiness by Time-Frequency Measures of EEG Signals

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Running title: EEG Time-Frequency Representation for Sleepiness Characterization

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ABSTRACT

Excessive daytime sleepiness (EDS) is one of the main symptoms of several sleep-related disorders with a great impact on patient lives. While many studies have been carried out in order to assess daytime sleepiness, automatic EDS detection still remains an open problem. In this work, a detection approach based on the time-frequency analysis of electroencephalography (EEG) signals is proposed. Multichannel EEG signals were recorded during five maintenance of wakefulness (MWT) and multiple sleep latency (MSLT) tests alternated throughout the day from patients suffering from sleep-disordered breathing. A group of 20 patients with EDS was compared with a group of 20 patients without daytime sleepiness (WDS) by analyzing 60-s EEG windows in the waking state. Measures obtained from the Choi-Williams distribution (CWD) and the cross-CWD were calculated in the EEG frequency bands δ (0.1-4 Hz), θ (4-8 Hz), α (8-12 Hz), β (12-30 Hz), and total band (TB, 0.1-45 Hz). Statistical differences between EDS and WDS groups were found in the δ and θ bands during MWT events ($p < 0.0001$). The results show that the EDS group presented more power in the θ band, while the WDS group presented higher spectral and cross-spectral entropy in the frontal zone in the δ band. In general, CWD and cross-CWD measures yielded sensitivities and specificities of above 80%. The area under the receiver operating characteristic curve was above 0.85 for classifying EDS and WDS patients.

Keywords: Biomedical signal processing, Time-frequency representation, Electroencephalography, Excessive daytime sleepiness

3.3.4 Correntropy measures to detect daytime sleepiness from EEG signals

Correntropy measures to detect daytime sleepiness from EEG signals

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Abstract

Excessive daytime sleepiness (EDS) is one of the main symptoms of several sleep related disorders and has a great impact on patients' lives. While many studies have been carried out in order to assess daytime sleepiness, automatic EDS detection still remains an open problem. In this work, a novel approach to this issue based on correntropy function analysis of EEG signals was proposed in order to detect patients suffering from EDS. Multichannel EEG signals were recorded during five Maintenance of Wakefulness Tests (MWT) and Multiple Sleep Latency Tests (MSLT) alternated throughout the day for patients suffering from sleep disordered breathing (SDB). A group of 20 patients with EDS was compared with a group of 20 patients without daytime sleepiness (WDS), by analyzing 60s EEG windows in a waking state. Measures obtained from the cross-correntropy function (CCORR) and auto-correntropy function (ACORR) were calculated in the EEG frequency bands: δ , 0.1–4 Hz; θ , 4–8 Hz; α , 8–12 Hz; β , 12–30 Hz; total band TB, 0.1–45 Hz. These functions permitted the quantification of complex signal properties and the non-linear couplings between different areas of the scalp. Statistical differences between EDS and WDS groups were mainly found in the β

band during MSLT events (p -value < 0.0001). The WDS group presented more complexity in the occipital zone than the EDS group, while a stronger nonlinear coupling between the occipital and frontal regions was detected in EDS patients than in the WDS group. At best, ACORR and CCORR measures yielded sensitivity and specificity above 80% and the area under ROC curve (AUC) was above 0.85 in classifying EDS and WDS patients. These performances represent an improvement with respect to classical EEG indices applied in the same database (sensitivity and specificity were never above 80% and AUC was under 0.75).

Keywords: biomedical signal processing, complexity theory, correntropy, electroencephalography, excessive daytime sleepiness

3.3.5 Mutual information measures applied to EEG signals for sleepiness characterization

Mutual Information Measures Applied to EEG Signals for Sleepiness Characterization

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ABSTRACT

Excessive daytime sleepiness (EDS) is one of the main symptoms of several sleep related disorders with a great impact on the patient lives. While many studies have been carried out in order to assess daytime sleepiness, the automatic EDS detection still remains an open problem. In this work, a novel approach to this issue based on non-linear dynamical analysis of EEG signal was proposed. Multichannel EEG signals were recorded during five Maintenance of Wakefulness (MWT) and Multiple Sleep Latency (MSLT) tests alternated throughout the day from patients suffering from sleep disordered breathing (SDB). A group of 20 patients with excessive daytime sleepiness (EDS) was compared with a group of 20 patients without daytime sleepiness (WDS), by analyzing 60-second EEG windows in waking state. Measures obtained from cross-mutual information function (CMIF) and auto-mutual-information function (AMIF) were calculated in the EEG -. These functions permitted a quantification of the complexity properties of the EEG signal and the non-linear couplings between different zones of the scalp. Statistical differences between EDS and WDS groups were found in β band during MSLT events (p -value <0.0001). WDS group presented more complexity than EDS in the occipital zone, while a stronger nonlinear coupling between occipital and frontal zones was detected in EDS patients than in WDS. The AMIF and CMIF measures yielded sensitivity and specificity above 80% and AUC of ROC above 0.85 in classifying EDS and WDS patients.

Keywords: Biomedical signal processing, Complexity theory, Electroencephalography, EEG, Excessive daytime sleepiness, Mutual information.

3.3.6 Auditory and nociceptive stimuli responses in the electroencephalogram. A non-linear measures and time-frequency representation based analysis

Focus Theme – Original Articles

Non-linear Measures and Time-frequency Representation of Electroencephalogram Containing Auditory and Nociceptive Stimuli Responses

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Keywords

Non-linear dynamics, time-frequency analysis, EEG processing, evoked potential

Summary

Introduction: This article is part of the Focus Theme of *Methods of Information in Medicine* on "Biosignal Interpretation: Advanced Methods for Neural Signals and Images".

Objectives: An efficient way to investigate the neural basis of nociceptive responses is the analysis of the event-related brain potentials (ERPs). The main objective of this work was to study how adaptation and fatigue affect the ERPs to stimuli of different modalities, by characterizing the responses to infrequent and frequent stimulation in different recording periods.

Methods: In this work, series of averaged EEG epochs recorded after thermal, electrical and auditory stimulation were analyzed with time-frequency representation and non-linear measures as spectral entropy and auto-mutual information function. The study was performed by considering the traditional EEG frequency bands.

Results: The defined measures presented a statistical significance p -value < 0.01 and accuracy higher than 60% by differentiating windows of response to infrequent (I) and frequent (F) stimuli between the start and end of the EEG recording.

Conclusions: These measures permitted to observe some aspects of the subject's adaptation and the nociceptive response.

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3.3.7 Prediction of nociceptive responses during sedation by linear and non-linear measures of EEG signals in high frequencies

Prediction of Nociceptive Responses during Sedation by Linear and Non-linear Measures of EEG Signals in High Frequencies.

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Abstract. The level of sedation in patients undergoing medical procedures evolves continuously, affected by the interaction between the effect of the anesthetic and analgesic agents and the pain stimuli. The monitors of depth of anesthesia, based on the analysis of the electroencephalogram (EEG), have been progressively introduced into the daily practice to provide additional information about the state of the patient. However, the quantification of analgesia still remains an open problem. The purpose of this work is to improve the prediction of nociceptive responses with linear and non-linear measures calculated from EEG signal filtered in frequency bands higher than the traditional bands. Power spectral density and auto-mutual information function was applied in order to predict the presence or absence of the nociceptive responses to different stimuli during sedation in endoscopy procedure. The proposed measures exhibit better performances than the bispectral index (BIS). Values of prediction probability of P_k above 0.75 and percentages of sensitivity and specificity above 70% were achieved combining EEG measures from the traditional frequency bands and higher frequency bands.

Keywords. Biomedical signal processing, Electroencephalography, Sedation, Complexity Theory, Mutual information.

Chapter 4

Discussion and Conclusions

The more relevant conclusions and contributions, which have been derived from the research work done in the present doctoral thesis, are indicated and discussed in section 4.1. After a general discussion of the results, the main findings obtained with the application of the developed techniques in the EEG studies are discussed. The discussion section is then divided in the three main topics handled in this thesis for assessing different states of consciousness by EEG analysis: the nonlinear analysis of EEG signal, the automatic sleepiness detection study and the characterization and the prediction of the nociceptive responses for the sedation level assessment. As a conclusion, section 4.2 summarizes the most relevant contributions obtained with the results of this thesis. Some of the possible future works that can be made from the methods and the findings achieved in this thesis are point out in section 4.3.

4.1 Discussion of the results

This thesis describes the development of several nonlinear techniques based on time-frequency representation, correntropy and auto-mutual information function applied to the EEG signal in different states of consciousness. Firstly, a new method based on the signal envelope for removing peak and spike noise from biological signals was successfully designed and applied to simulated and real EEG signal. This new method was used in this thesis to remove this kind of noise, permitting to take into account EEG segments that, otherwise, would be rejected. Then, several studies were carried out in order to extract and evaluate EEG measures based on nonlinear techniques. In this way, it had been possible to analyze the advantages and the disadvantages of the EEG measures applied in different contexts. Beside the estimated non-linear techniques, a new method for calculating the entropy based on time-frequency representation was designed and evaluated on simulated and real EEG signals. In all the studies, the proposed measures were compared with the traditional EEG measures based on time-domain and frequency-domain analysis.

The purpose of all the analysis was to apply the developed techniques to EEG signal databases with different features. A distinctive characteristic of most physiological systems is their complexity, due in part to the interaction with other physiological system units with complex feedback loops. Accordingly, it is expected that the dynamics of these systems, and especially of the physiological signal which are output of these systems, have a nonlinear and non-stationary behavior. Because of that, they require analysis and characterization involving techniques that take into account their non-stationarity, associated with techniques derived from complexity theory. The results presented in this thesis confirm that a simple statistical measure is not sufficient to describe the different behavior of these kinds of signals. Therefore, it is necessary to have a variety of measures in order to characterize different aspects of the physiological systems.

In general, it can be noted that in each performed study the measures based on mutual information (AMIF or CMIF) and correntropy (ACORR or CCORR) have better statistical

performances than the traditional measures or the measures obtained with time-frequency representation. This demonstrates the improvements of the non-linear methods due to the capability of mutual information and correntropy functions of characterizing non-linear features of the EEG signal, which traditional measures cannot detect.

The following sections contain a more detailed discussion of the different studies that has been carried out in this thesis.

4.1.1 Nonlinear analysis of EEG signal

The evaluation of the developed techniques applied to simulated and real EEG signals permitted to individuate which measures can give more information about their nonlinear content. Particularly, the results of the new nonlinear techniques applied to time-frequency representation (TFR) have indicated that the instantaneous spectral entropy becomes higher when the spectrum of the signal contains many frequency components or tends to be close to the spectrum of white noise. On the other hand, analyzing the auto-mutual information (AMIF) measures, in general, the local maximum and the first decay were able to detect changes in the nonlinear dynamics of the time series in the best way. Also, the mean frequency of the correntropy power spectral density was able to characterize the nonlinear behavior of the EEG signals.

The results of the instantaneous entropy and spectral information entropy measures have shown that their values tend to decrease, with different proportion, when the behaviors of the synthetic signals evolve from chaos or randomness to periodicity. This methodology takes advantage of the property inherent to TFR that permits to deal with non-stationary signals together with the property of Shannon entropy that deals with chaoticity, complexity and randomness. In this way, they can be useful tools to quantify the different periodic, chaotic and random components in physiological signals.

In each of the studies, the combination of maximum four non-linear measures based on TFR, AMIF and correntropy permitted to characterize with high statistical significance the changes in EEG produced by the different level of sleepiness, different type of nociceptive stimulus and level of sedation. The performances of AMIF depended on the choice of the parameter q in each of the study. Several tests were carried out using a big range of q values, in this way it could be possible to study how both smallest and largest probability influence the quantification of the complexity behavior and the coupling in EEG signal. It can be denoted that in most of the studies, the measurement of the first decay and the first local maximum of AMIF and the spectral density of the correntropy gave the best contribution in order to describe the complexity features of the EEG signal.

4.1.2 Automatic sleepiness detection

The application of the developed techniques in the study of automatic sleepiness detection demonstrated that the power in θ band in awaking state and in frontal zone (F3) is higher ($p\text{-value}<0.005$) in the group with excessive daytime sleepiness (EDS) during MSLT trials, when the patients had explicit instruction to try to fall asleep. Different behavior of the measures was observed between MWT and MSLT trials, close to the sleep onset in frontal zone. These might be due to the fact that in MSLT trial both groups closed the eyes, while in MWT trials, when they tried to stay awake, patients without daytime sleepiness (WDS) were widely in eyes opened condition. This is also associated with differences in the EEG bands and in ocular

movements, produced by the tasks of staying awake, which reflect different sleepiness states between the two groups. The status of the eyes is important because, for example, a posterior α rhythm that appears typically with the eyes closed, would not be recorded during the MWT, which is typically recorded with the eyes open. However, in this study the results of the MWT were not compared with those of the MSLT, but instead the time evolution of the EEG signals in each of the two tests was analyzed.

From CWD results, it can be noted that the spectral complexity in awaking state is higher in WDS group than EDS in the frontal zones (F3). Similarly in a previous study (Inouye *et al.*, 1991), spectral entropy has been applied to measure the irregularity of the EEG during rest and mental arithmetic tasks, with results showing that EEGs during rest were significantly more irregular anteriorly than in the occipital areas. Furthermore, Fell *et al* (1996) have shown that instantaneous spectral entropy is a useful discriminator of sleep stages, as its value decreases significantly during different stages of sleep. The best CWD measures have higher values of sensitivity (*Sen*), Specificity (*Spe*), and area under ROC curve (*AUC*) than the best traditional measure based on time-domain analysis and frequency-domain analysis. This demonstrates the improvements in the time-frequency method due to the capability of time-frequency functions to characterize non-stationary EEG features that traditional measures cannot detect. Among the time-frequency techniques, CWD spectral entropy in F3 channels in δ band and CWD power in F3 channel in θ band gave the highest *Sen*, *Spe* and *AUC* in the discrimination of EDS and WDS patients in all the studies. These measures outperformed the traditional EEG measures yielding about 10% more of *Sen* and *Spe* and 0.15 more of *AUC*.

Different complexity behavior between EDS and WDS patients was found in β band in the occipital zones. AMIF results demonstrated that in windows when patients are awake this complexity is higher (p-value<0.005) in WDS group than EDS during MSLT. A different behavior of the non-linear measures was observed along all the MWT and MSLT naps: while the WDS group presents changes in complexity behavior between MWT and MSLT, the EDS group maintains a low complexity for both MWT and MSLT. Regarding the correntropy function, the power spectrum of ACORR in β band presents lower frequencies in EDS group than WDS when patients are awake during MSLT in the occipital zones (p-value<0.005). The behavior of this measure in WDS patients has a regular tendency during the whole day. This measure shows almost the same mean value in all MWT trials, always lower than the mean value of all MSLT trials. In this way, it can be assumed that these measures are able to reflect the physiological changes between the different conditions of the MWT and MSLT trials and to characterize the different sleepiness levels of the EDS and WDS groups. Analyzing the time evolution of the AMIF measures in each trial, it can be noted that the complexity decreases with time presenting similar slope when the sleep onset is approached for both EDS and WDS patients. In the MSLT, there are differences between groups during the previous minutes to the appearance of the sleep onset, whereas after sleep onset both groups reduce the complexity of the signal. Then, the differences between groups are reduced close to the sleep onset that implies a reduction of the complexity of the β band in both groups. In the MWT nap, the complexity is lower in the groups EDS but statistically differences was only observed near the sleep onset (from -100 s to +100 s), where the decrease of EDS complexity has a slope higher than the WDS. From the comparison of the results between mutual information and correntropy, it can be noted that ACORR, applied to a single channel, gave slightly better statistical performances in term of complexity characterization than AMIF, while CMIF applied between two channels outperforms CCORR in term of nonlinear coupling assessment.

Finally, it can be stated that the presented methodology could help to detect sleep onset in an automatic way so well as standard criteria (visual analysis), for routine diagnostic MSLT or

MWT but also to detect and warn when someone is at risk of falling asleep, as a drowsiness detectors in cars as a system to help driving safer.

4.1.3 Characterization and prediction of pain responses for the sedation level assessment

Auto-mutual information function and measures obtained from time-frequency representation have allowed the responses of infrequent (I) and frequent (F) stimulations in thermal, electrical and auditory stimuli to be characterized. Statistical analysis has revealed some significant differences in those measures calculated in different periods of the EEG recording. The complexity differences between infrequent and frequent stimulations were only seen in δ band, where the potential was more evidenced. Also, the aspects of the adaptation of the subjects observed from *Start* to *End* of the recording time were evidenced in δ band. By comparing I and F , the complexity behavior was similar for auditory and electrical stimulation at *Start* ($I > F$) and also at *End* ($I > F$) of the recording time, being contrary the behavior of the thermal stimuli ($I < F$). Furthermore, the latency of the peak of power for all frequency bands was delayed in I respect to F . Finally, time-frequency representation and auto-mutual information function techniques may prove helpful in order to characterize aspects of the adaptation of the subjects and nociceptive response information. In a similar way, a previous work (Melia *et al.*, 2011) demonstrated that measures based on Choi-Williams distribution (CWD) are helpful in the characterization of the mismatch negativity component (MMN). The statistical analysis reveals some significant differences in the CWD defined measures between response to frequent and infrequent stimulus, showing that instantaneous power could better separate MMN component from noise.

The results of these studies could give a strong contribution in the automatic detection of the nociceptive change and assessment of the abnormal brain function in chronic pain conditions and especially in the characterization of the nociceptive responses during sedation. The proposed method can be applied for studying in different sedation levels the responses to several frequent or infrequent nociceptive stimuli induced during surgical procedures, such as the endoscopy tube insertion, the surgical incision, etc.

Regarding the prediction of pain responses during sedation based on EEG, the combination of four measures in the traditional EEG bands permitted to yield $Pk > 0.8$ when discriminating between $RSS < 5$ and $RSS \geq 5$ and predicting the gag reflex. However, when discriminating between $RSS < 6$ and $RSS = 6$ or between $RSS = 5$ and $RSS = 6$, it is necessary to use also measures from EEG filtered at high frequency bands (HF ; 60-95 Hz and VHF ; 105-145 Hz) in order to obtain $Pk > 0.75$. In all the performed trials, the combinations of four EEG measures yielded discrimination performances better than BIS (T-student test, p-value < 0.0001) in the prediction of pain responses. It is worth noting that the BIS index integrates several EEG measures such as a time domain, frequency domain, and high order spectral parameters into a single variable. In this way, in order to make an appropriate comparison between the BIS and the results of the present study, the multi-variable analysis of EEG measures should be taken into account. However, it can be noted that only one measure ($Pk = 0.72$) calculated on EEG filtered in VHF is enough to outperform BIS ($Pk = 0.62$) when discriminating between $RSS = 5$ and $RSS = 6$. It is well known that BIS is able to describe hypnotic effect. However, the proposed multi-variable functions showed a better capability than BIS to describe the analgesic effect. The presence of analgesic, remifentanyl in this case, causes that the patient can not react to painful stimuli but has a low level of sedation (i.e. a high BIS value). If only propofol were dispensed,

its concentration would have to be higher in order to block painful stimuli and that would produce very low BIS values.

The hardest challenge is the discrimination between sluggish response (RSS=5) and no response (RSS=6). The best results in the discrimination between RSS=5 and RSS=6 were given by the combination of measures based on the mean frequency in α band, the local maximum of the AMIF calculated with $q>1$ in HF (60-95 Hz) band and the first decay of AMIF calculated with $q<1$ in VHF (105-145 Hz) band. In general, the major benefits in the discrimination of these two RSS levels are provided by studying changes in the power spectral density in α and β bands of EEG and in the complexity behavior of EEG filtered in high frequencies band (60-95 Hz and 105-145 Hz). In order to yield high performances in the prediction of other stimuli responses, the complexity behavior of δ and θ bands and the power spectral density in VHF should also be taken into account. In this last analysis of the sedation level assessment, the time-frequency representation was not applied and only the traditional Welch method was used in order to calculate the spectral measures. Comparing the results of two previous works, applied to the same database, it can be noted that the statistical performances of the measures based on time-frequency representation (Melia *et al.*, 2013) does not significantly improve the statistical performances of measures based on the Welch method (Melia *et al.*, 2014a). In this way, since the Welch method avoids excessive computational charges and requires less computing time, it was considered to better fit with the purpose of this study. This will help in the designing of an overall diagnostic indicator that can quickly indicate changes in the state of the patient.

In a previous work, spontaneous frontal electromyography (SEMG) has been shown to be a useful indicator of pending arousal (Yli-Hankala *et al.*, 1994). Sudden increases in the amplitude of SEMG activity in frontal muscles during surgery indicated enhanced patient responsiveness (Chang *et al.*, 1998). This is due to the motor innervation of the upper facial muscles, which arises from the brainstem, with connections to vigilance centers in the reticular formation. Some successful applications of the SEMG on the detection of arousal during anesthesia have been published (Yli-Hankala *et al.*, 1994; Poison *et al.*, 1995; Chang *et al.*, 1998). Due to great inter-individual variability in the amplitude of the SEMG, this technique has not gained wide clinical acceptance. In this work, the computed AMIF normalized by the maximum value permits to obtain nonlinear measures that might limit the inter-individual variability.

The contraction strength of a frontals muscle is linearly dependent on the firing rate of motoneurons, which innervate the frontals. As surface electrodes measure the sum of signals from multiple motor units, the work of Rautee *et al.* (2004) suggested that the complexity of the SEMG band is related to the level of desynchronization between firing rates among adjacent motor units. The results of spectral entropy in that study demonstrated that increased firing rates seem to produce increased desynchronization between motor units (Rautee *et al.*, 2004) associated with higher disorder of the system. From the results of the present thesis, it can be assumed that the less complexity behavior of the EEG filtered at VHF might be associated with a decrease of the firing rates of the SEMG induced by the deeper level of sedation.

Regarding the traditional EEG bands, previous studies have been demonstrated that increased sedation levels are marked by increased δ and θ power and frontal α with increased peak frequency (Gugino *et al.*, 2001; Hindriks R and van Putten, 2002; Feshchenko *et al.*, 2004; Ching *et al.*, 2010). Then, increasing propofol concentration in human subjects shifts cortical activity from a high-frequency, low-amplitude signal to a low-frequency, high-amplitude signal. Specifically, β activity decreases and α and δ activities increase (Feshchenko *et al.*, 2004) with increasing levels of propofol anesthesia. In the present thesis, it was found that P_β is lower for the unresponsive state reflecting a higher level of sedation respect unresponsive states. Also the

mean frequency in α band is lower for $RSS=6$, this implies that the spectral power is higher in lower frequencies. Furthermore, patients in deep sedation showed a more complex EEG activity in low frequency bands than patients in lower sedation levels. This can be related with the fact that EEG activity becomes slower as the sedation level increases, and thus, it is expected that patients in unresponsive state present a slower EEG signal than responsive state, increasing the signal complexity in low frequency bands. Power in the high-frequency component of EEG signals corresponds to corticocortical activity (Gray and Mc Cormick, 1996), while power in the low-frequency component of EEG signals primarily arises from subcortical interactions (McCormick *et al.*, 1997). The decrease in high-frequency power with the administration of propofol may be due to a decrease in intracortical and corticocortical activity. The increase in low-frequency power may arise from interactions with subcortical structures such as the thalamus (Velly *et al.*, 2007; Ching *et al.*, 2010). EMG activity reflects subcortical activity during general anaesthesia. According to previous studies, subcortical structures could be a site of the analgesic effect of anaesthetics (Savola *et al.*, 1991; Antognini *et al.*, 1993; Collins *et al.*, 1995).

Analyzing all the results related to the prediction of pain responses, it can be denoted that the combinations of linear and nonlinear measures calculated in the traditional EEG bands were able to yield $Pk>0.8$ when discriminating between $RSS<5$ and $RSS=5$ and/or $RSS=6$ and between GAG 0 and GAG 1. However, in order to yield $Pk>0.8$ when discriminating between $RSS<6$ and $RSS=6$, measures calculated in the traditional EEG bands had to be combined with measures calculated in EEG filtered at high frequencies where the SEMG component is present.

Regarding the individual factors, the age and gender does not influence the results of the EEG measures in a significant way. After performing the statistical analysis of the measures divided in subgroups based on age and gender, it was observed that the *Sen* and *Spe* had a change of less than 3%. Furthermore, the influence of the SNP A118G in OPRM1 on the prediction of the response to pain stimulation based on EEG measures was evaluated in a preliminary study (Melia *et al.*, 2014b) by taking into account the subset of two groups of patients with and without the SNP, observing an improve of the statistical performances of the EEG measures in the prediction of responding to nail bed compression when the presence or absence of the SNP was taken into account. The combination of the propofol concentration (*CePropo*) with the spectral power and auto-mutual information measures in δ and β bands yielded $Pk>0.8$ in the group without SNP and $Pk>0.9$ in the group with SNP. However, only the discrimination between $RSS\leq 5$ and $RSS=6$ was performed and the quantity of the analyzed windows in the set of patients with SNP was low; then, these preliminary results need further validation with a higher number of patients.

In conclusion, the measures calculated in EEG filtered at high frequencies improved the prediction of unresponsive ($RSS<6$ and $GAG=0$) and responsive ($RSS=6$ and $GAG=1$) states when different types of stimuli are taken into account.

4.2 Conclusions of the thesis

The most important contributions of this thesis include the development and test of new nonlinear measures based on time-frequency representation, mutual information functions and correntropy. These measures were applied to EEG signal recorded in different state of consciousness providing additional information that helped to improve the automatic sleepiness detection, the characterization and prediction of the nociceptive responses and thus the assessment of the sedation level. In summary, the main contributions are:

- Design, optimization and testing of a new methodology to reduce peak and spike artifacts based on the analytic signal envelope (ASEF algorithm).
- Development and testing of nonlinear measures based on time-frequency representation, mutual information functions and correntropy in order to characterize the complexity characteristics of the EEG signal.
- Development and evaluation of a new method used to calculate the instantaneous spectral entropy and the spectral information entropy applied to the Choi-Williams distribution.
- Design of a methodology based on the developed techniques for the automatic sleepiness detection in patients suffering sleep disorders which improved the traditional EEG analysis.
- Characterization of the EEG responses to infrequent and frequent thermal, electric and auditory stimulation in a different recording period by the application of the developed techniques.
- Obtaining of a set of EEG measures based on the developed techniques applied to EEG filtered in the traditional band and in higher frequency bands that improve the prediction of the nociceptive response during sedation.

4.3 Future work

Among the developed techniques, the instantaneous entropy and spectral information entropy was only applied to one EEG database, so that the immediate future extensions will be the application of these techniques in the studies of sleepiness detection and in the characterization and prediction of the nociceptive responses. Furthermore, also the correntropy function needs to be evaluated in the prediction of the nociceptive response during sedation.

Besides the application of correntropy, in order to develop an index capable to predict nociceptive responses during sedation, further validations have to be done before introducing it in the clinical practice. First of all, higher frequency ranges of EEG might be explored in order to asses which frequency bandwidth, in EMG range, might give the best benefit in this kind of study. Then, the combination of measures that gave the best prediction performances has to be validated by designing an index using a training subset of patients and by evaluating it on another subset of patients.

Once obtaining a validated index able to predict the pain responses, the effects on the EEG produced by the nociceptive responses during surgical procedures need to be studied. The same methods used in the characterization of the EEG pain responses in healthy subjects, will be applied to EEG segments recorded, for example, during or after the tube insertion or the surgical incision. This will permit to further characterize the different EEG responses to nociceptive stimulation associated with different sedation levels. In this way, it will be possible to detect, along the all surgery period, the changes in the EEG signal related to the different balances between the pharmacological actions and the surgery aggressiveness. This will give a further contribution in the improvement of the sedation level assessment.

Regarding the ASEF algorithm, an interesting future work would be the optimization of the algorithm parameters for the application to a different kind of physiological signals such as heart rate variability signal (HRV), electromyogram (EMG), etc.

One limitation of the results obtained in the automatic detection of sleepiness is that a retrospective study needs to be designed, including data recorded from a greater number of patients. This future work would permit the development of an index for the automatic detection of excessive sleepiness based on a combination of nonlinear EEG measures.

Finally, the application of the techniques developed in this thesis is not subject only to studies of EEG signals, for that their use has to be considered in other applications or in other type of signals as they can be: the assessment of different diseases by EEG analysis, the study of the autonomous nervous system by HRV signal, the EMG analysis, etc.

Appendix A

Publications derived from this doctoral thesis

A.1. International Journal indexed in the Journal Citation Report

- Melia U., Vallverdú M., Clariá F., Gallardo J.J., Perera A. and Caminal P., (2013). “Choi-Williams Distribution to Describe Coding and Non-coding Regions in Primary Transcript Pre-mRNA,” *Journal of Medical and Biological Engineering*, vol. 33, no. 5, pp. 504–512.
- Melia U., Vallverdu M., Clariá F., Valls-Sole J. and Caminal P., (2014) “Auditory and Nociceptive Stimuli Responses in the Electroencephalogram. A Non-linear Measures and Time-frequency Representation Based Analysis,” *Methods of information in medicine*, vol. 53, no. 4.
- Melia U., Clariá F., Vallverdu M. and Caminal P., (2014) “Filtering and Thresholding the Analytic Signal Envelope in order to improve Peak and Spike Noise Reduction in EEG Signals,” *Medical Engineering & Physics*, vol. 36, no.4, pp. 547–553.
- Melia U., Clariá F., Vallverdu M. and Caminal P., (2014) “Measuring Instantaneous and Spectral Information Entropies by Shannon Entropy of Choi-Williams Distribution in the context of Electroencephalography,” *Entropy*, vol. 16, no. 5, pp. 2530–2548.
- Melia U., Guaita M., Vallverdú M., Clariá F., Montserrat J. M., Vilaseca I., Salamero M., Gaig C., Caminal P. and Santamaria J., (2014) “Characterization of Daytime Sleepiness by Time-Frequency Measures of EEG Signals,” *Journal of Medical and Biological Engineering*, doi:10.5405/jmbe.1823.
- Melia U. Guaita M., Vallverdu M., Montserrat J. Vilaseca I., Salamero M., Gaig C., Caminal P. and Santamaria J., (2014) “Correntropy measures to detect daytime sleepiness from EEG signals,” *Physiological Measurement*, vol. 35, no. 10, pp.2067–2083.
- Melia U., Vallverdú M. (2014) BOOK REVIEW: *Methods in Brain Connectivity. Inference through multivariate time series analysis.* Authors: Koichi Sameshima and Luiz Antonio Baccalá *Frontiers in Neuroengineering* CRC Press, Taylor & Francis Group. Boca Raton, FL. USA ISBN 978-1-43984-5721, *Clinical Neurophysiology*, vol.1.
- Melia U., Guaita M., Vallverdu M., Embid C., Vilaseca I., Salamero M., Caminal P. and Santamaria J., (2014) “Mutual Information Measures Applied to EEG Signals for Sleepiness Characterization,” *Medical Engineering & Physics* (under review).
- Melia U., Vallverdú M., Borrat X., Jospin M., Jensen E. W., Valencia J. F., Gambus P. L. and Caminal P., (2014) “Prediction of Nociceptive Responses during Sedation by Linear and Non-linear Measures of EEG Signals in High Frequencies,” *Journal of Neural Engineering* (under review).
- Guaita M., Melia U., Vallverdu M., Embid C., Vilaseca I., Salamero M., Caminal P. and Santamaria J., (2014) “Regularity of cardiac rhythm as a marker of sleepiness in sleep disordered breathing,” *PlosOne* (under review).

A.2. International conferences

- Julitta B., Vallverdu M., Melia U., Tupaika N., Jospin M., Jensen E.W., Struys M.M.R.F., Vereecke H.E.M. and Caminal P. (2011) “Auto-Mutual Information Function of the EEG as a Measure of Depth of Anesthesia,” *33th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, vol.1, pp. 2574–2577.
- Melia U., Vallverdú M., Clariá F., Casanova J., Valls-Solé J. and Caminal P., (2011) “Time-Frequency Characterization of Mismatch Negativity in Nociceptive Responses,” *33th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, vol. 2, pp. 7719–7722.
- Melia U., Clariá F., Vallverdú M. and Caminal P., (2012) “Removal of peak and spike noise in EEG signals based on the analytic signal magnitude,” *Proceedings of the 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, San Diego, USA, vol. 1, pp.3523–3526.

Appendix A. Publications derived from this doctoral thesis

- Melia U., Guaita M., Vallverdú M., Clariá F., Caminal P., Embid C., Vilaseca I., Salamero M., and Santamaria J., (2013) “Non-linear dynamic analysis of RR signals in patients with and without Excessive Daytime Sleepiness,” *Computing in Cardiology, Zaragoza*, pp. 449–552.
- Paternoster L., Vallverdú M., Melia U., Clariá F., Voss A. and Caminal P., (2013) “Analysis of Epileptic EEG Signals in Children by Symbolic Dynamics,” *Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS), Osaka, Japan, 3 - 7 July*, pp. 4362– 4365.
- Melia U., Vallverdú M., Jospin M., Jensen E. W., Valencia J. F., Clariá F., Gambus P. L. and Caminal P., (2013) “Prediction of Nociceptive Responses during Sedation by Time-Frequency Representation,” *Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS), Osaka, Japan, 3 - 7 July*, pp. 2547–2550.
- Melia U., Vallverdú M., Jospin M., Jensen E. W., Valencia J. F., Clariá F., Gambus P. L. and Caminal P., (2013) “Auto-Mutual Information Function for Predicting Pain Responses in EEG Signals during Sedation,” *XIII Mediterranean Conference on Medical and Biological Engineering and Computing 2013, MEDICON 2013, 25–28 September 2013, Seville, Spain, IFMBE Proceedings 41*, p. 623–626.
- Melia U., Vallverdú M., Jospin M., Jensen E. W., Valencia J. F., Gambus P. L., Perera A. and Caminal P., (2014) “Interaction between EEG and Drug Concentration to Predict Response to Noxious Stimulation During Sedation-Analgesia: Effect of the A118G Genetic Polymorphism,” *Proceedings of the 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS), Chicago, USA, 26–30 August, Invited session paper*.
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