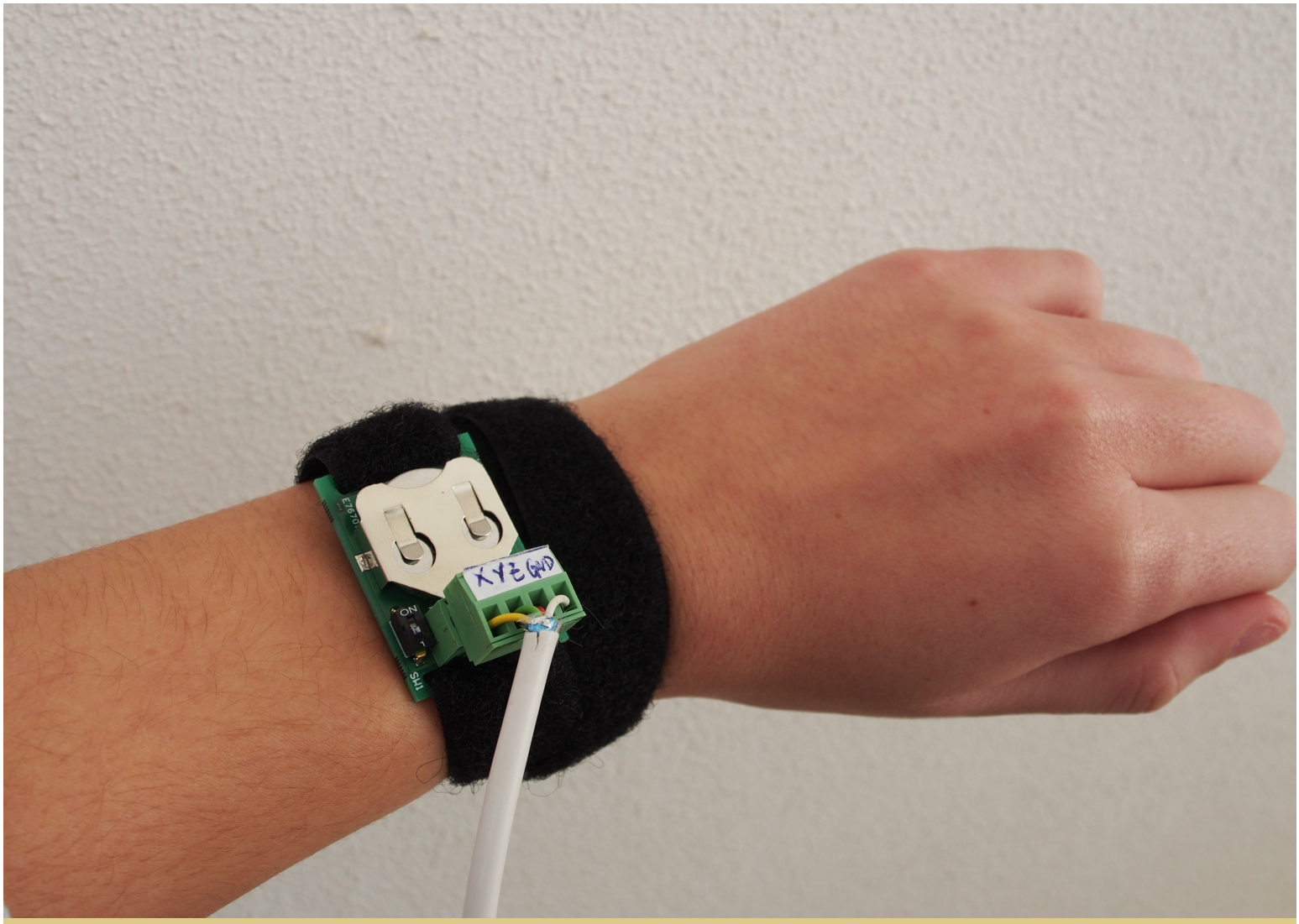

Mariana Ferreira Ramos

CHARACTERIZATION AND DETECTION OF EPILEPTIC SEIZURES BASED ON ACTIGRAPHY DATA

Thesis submitted in fulfilment of requirements for the degree of Mater in Physics Engineering, presented at Faculty of Sciences and Technology of University of Coimbra, in collaboration with Institute for Systems and Robotics and Hospital Santa Maria in Lisbon under the supervision of Prof. Dr. João Miguel Sanches, Drª. Carla Bentes and Prof. Dr. Custódio Loureiro.

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MASTER THESIS

Characterization and detection of epileptic seizures based on actigraphy data

Author:
Mariana RAMOS

Supervisors:
Prof. João SANCHES
Doutora Carla BENTES
Prof. Custódio LOUREIRO

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Anyone who has never made a mistake has never tried anything new.

Albert Einstein

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Abstract

Epilepsy is a severe medical condition affecting millions of people in the world. Detection and prediction of epileptic events is an open problem and an active field of research in the medical and neuroscience communities.

Patients with epilepsy are monitored at the service of Neurology from the Hospital de Santa Maria in Lisbon for long periods where huge amount of data, such as EEG, ECG and video, is collected in order to capture the appropriated number of epileptic episodes needed to characterize the disease. These episodes, impossible to predict, are random and sparse in time which makes the task of analysis difficult and time consuming.

In this thesis an actigraphy device (an accelerometer) was designed and assembled to be plugged into the amplifier used in the hospital to collected the EEG signals. This way the activity of the patient on his non-dominant wrist (usually the left one) is recorded and stored simultaneously with the other signals acquired during the exam avoiding to perform the usual complex procedure of signal alignment and sampling frequency adjustment.

Algorithms for detection of specific movement patterns were designed in order to automatically detect epileptic seizures with associated movement disturbances. The goal is to perform an automatic annotation of the data collected during exam and help the technical staff in its analysis. In the future these algorithms will be used in ambulatory systems to identify and record epileptic seizures in normal life conditions of the patients.

Two prototypes were produced and tested at the hospital with real patients and the algorithms for movement detection and epileptic seizure identification were designed, implemented and tested using synthetic and real data. The EEG data from the patients were annotated and classified manually by the technicians where all the paroxysmal events were identified and used for training and testing as ground truth information.

A total of 62 events from 4 patients, checked by the medical doctor, where used to train the detector and validate the algorithm. An accuracy of more than 98% was achieved in detecting movements and among them more than 84% were correctly classified as epileptic seizures.

The two prototypes are installed at the hospital where more data are being collected.

Keywords

Epilepsy, electroencephalography, accelerometer, seizures, detection, actigraphy

Resumo

A epilepsia é uma condição médica grave que afeta milhões de pessoas no mundo. A detecção e previsão de crises epilépticas é um problema em aberto e um campo ativo de pesquisa nas comunidades médica e de neurociência. Os pacientes com epilepsia são monitorizados no serviço de Neurologia do Hospital Santa Maria em Lisboa durante longos períodos, durante o qual uma grande quantidade de dados, tais como EEG, ECG e vídeo, é recolhida a fim de detectar o número necessário de crises epilépticas necessário para caracterizar a doença. Estes episódios, impossíveis de prever, são aleatórios e dispersos no tempo o que torna a tarefa de análise difícil e demorada. Nesta tese foi projetado e montado um dispositivo de actigrafia (um acelerómetro) para ser conectado ao amplificador usado no hospital para adquirir os sinais de EEG. Desta forma, a actividade motora do paciente é gravada e armazenada simultaneamente com os outros sinais adquiridos durante o exame evitando a realização do procedimento habitual e complexo de alinhamento de sinal e ajuste da frequência de amostragem, usando o dispositivo no pulso não-dominante (usualmente a esquerdo). Dois algoritmos para detecção de padrões de movimento específicos foram concebidos a fim de detectar automaticamente crises epilépticas com distúrbios de movimento associados. O objetivo é realizar uma anotação automática dos dados recolhidos durante o exame e ajudar os técnicos na análise. Futuramente, estes algoritmos iram ser utilizados em sistemas ambulatórios para identificar e registar as crises epilépticas em condições normais de vida dos pacientes. Dois protótipos foram produzidos e testados no hospital com pacientes reais e os algoritmos de detecção de movimento e identificação de crise epiléptica foram concebidos, implementados e testados utilizando dados sintéticos e reais. Os dados de EEG adquiridos nos pacientes foram anotados e classificados manualmente pelos técnicos nos quais foram identificados e utilizados para treino e testes todos os eventos paroxísticos.

Um total de 62 eventos adquiridos a partir de 4 pacientes, verificados pelo médico, foram utilizados

para treinar o detector e validar o algoritmo. Uma precisão de superior a 98% foi atingida na detecção de movimentos e entre eles mais de 84% foram corretamente classificados como crises epilépticas. Os dois protótipos estão instalados no hospital onde mais dados estão a ser adquiridos.

Palavras Chave

Epilepsia, electroencefalografia, acelerómetro, crises, detecção, actigrafia

Contents

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Abbreviations

CMRR-Common-mode rejection ratio

MEMS-Microelectromechanical system

WBM-Wet bulk machining

CMOS-Complementary metal-oxid-semiconductor

IC-Integration circuits

DC-Direct current

AC-Alternative current

ACM-Accelerometer

VCC-IC power-supply pin

GND-Ground

EEG-Electroencephalography

ECG-Electrocardiogram

EMG-Electromiography

EOG-Electrooculography

ADC-Analog-to-digital converter

FIR-Finite impulse response

RMS-Root mean square

MD-Movement detection

TP-True positive

TN-True negative

FP-False positive

FN-False negative

LTI-Linear time invariante

List of Symbols

Si-Silicon

g-Unit of acceleration equals to Earth's gravity at sea level

m/s^2-meters per second squared

Hz-Hertz

K-Kilo

C-Capacitance

A-Area

d-Distance

ϵ-Permitivity of the material

V-Voltage

μ-Micro

K_s-Spring constant

x-Related distance

Δ-Difference

$\frac{d}{dt}$-Derivate

F-Frequency

$\tilde{X}$-Normalized value

s-Seconds

r_{yx}-Crosscorrelation

1

Introduction

Contents

1.1 Motivation

Epilepsy is a complex brain disorder characterized by the recurrent seizures that manifest themselves in several ways such as motor behaviours or muscles twitches, sensitive or sensorial experiences and autonomic manifestations. These features represent a big interest for this study. Epileptic seizures are characterized by changes of physiological or behavioural patterns that can be used to identify an epileptic seizure.

Epileptic seizures can also be associated with neurocognitive impairment, lower levels of school performance, other neurological disorders and an increased risk of trauma or even sudden onset death. In addition, the financial and social costs associated with the chronic uncontrolled seizures to the patient and his family are high. So, epileptic seizure detection provides the capacity to allow early and correct treatment, can represent an important clinical tool.

Nowadays, the gold standard method to detect epileptic seizures is Video and EEG temporally synchronized. The analysis of the data acquired from a patient for a week is made by a technician at a early stage. He analyses all data for twenty four hours at time and marks all events such as seizures or possible seizures which is a time consuming work. After that, the doctor will analyse the events marked by technician and he will assess all events marked earlier.

In the current study, a tool which has been already used in other neurological disorders and even in epilepsy is proposed with a different manner of use. An accelerometer is placed in the wrist with the purpose to detect motor movements during the seizures. This device may help detect epileptic seizures and also reduce the work time required to analyse the EEG data during long-term epilepsy monitoring. The main goal of this study is to ease the work of the doctors and technicians who assess the results of the long-term EEG monitoring. Thus, the developed device will be connected through the same acquisition equipment which the EEG (electroencephalography) electrodes are connected, setting aside the need to synchronize them.

It is true that the video gives almost the same information. However, the ACM (accelerometer) signals are easier to process than video. We believe that these signals represent a big advantage in epilepsy patients monitoring. Since these signals can be measured by a commercial accelerometer separately and afterwards visually synchronized, which does not represent an very accurate method, we believe that developing a device which will be connected through the same acquisition unit together

with all other signals can represent a big advantage.

In a first stage, the device will be installed in the neurological department in Hospital Santa Maria, in Lisbon. All experimental tests will be done with patients who are followed in this hospital department for epilepsy monitoring.

Since this disease affects a lot of people worldwide and it is much more common than ones thinks, this study can provide a good additional tool for both patient and doctor.

1.2 State of The Art

Epilepsy is one of the most common neurological disorders in the world. It is characterized by recorrent burst of abnormal brain function. These "bursts" are known as epileptic seizures[9].

The patient is not the only one affected by the disorder but also family and friends suffer the resulting consequences. Epilepsy is closely associated with psychological and social consequences.

The aetiology of the disease can be unclear which can be a problem as knowledge of the cause is a very important step towards an accurate management of the disease. In the next chapter the process of epilepsy's characterization will be discussed in more detail.

In recent years, the definition of epileptic seizure has been discussed by *International League Against Epilepsy* (ILAE) and the *International Bureau for Epilepsy* (IBE). They have reached a consensus and the definition formally accepted by ILAE and IBE is that an epileptic seizure is a brief occurrence of signs or symptoms due to abnormal neuronal activity of the brain.[9] In fact, an epileptic seizure is a transient paroxysmal event as a result from an excessive discharge of a set neurones in the brain leading to clinic manifestations[10]. An epileptic seizure is transient and demarcated on time with an onset and offset. The most accurate method known to assess the onset and the termination of an electrical discharge in the brain is the EEG. Nevertheless, an ictal electrical discharge may start in a set of neurones and may be spread through the brain before it becomes clear in EEG. Furthermore, the clinical changes may be seen before or can be more clearly observed than EEG changes or vice versa. Therefore, a time lag may exist between the onset of seizures in the EEG and the onset of clinical changes. In order to identify these onsets temporally synchronized Video and EEG is used. With this technique (video-EEG monitoring) it is possible to define that EEG changes often appear first.

Furthermore, it is important to follow a set of steps in order to achieve a correct treatment in which the aim is a decrease of seizures. Firstly the aetiology must be found, secondly, a correct classification of the type of epilepsy must be done, and finally choosing the correct treatment must be choosen. All these steps will be described deeply in the next chapter.

1.2.1 Clinical manifestations

To classify an epileptic seizure more accurately, it is important to know more about the clinical symptoms or signs related to it.

An epileptic discharge can be focal or generalized, depending if the epileptic seizure begins in a limited part of one of the hemispheres of the brain or whether it begins simultaneously in extensive cortical regions. [11] It is estimated that 60% or more of the epileptic patients have focal epilepsy [12] and 60% of the partial seizures set off in the temporal lobes [13]. Partial seizures can be subdivided into three groups: simple partial (i.e. focal seizures in which consciousness is preserved), complex partial (in which the consciousness is impaired) and partial with secondary generalisation.

Any function controlled by the brain may be disturbed whether or not the electric discharge has affected the area of the brain that it controls. The symptoms or signs that occur as a result of this abnormal activity can be sensory, motor, autonomic, cognitive, behavioural or psychological. In this case study, we are more interested in motor and autonomic signs. It is therefore of considerable interest to know that motor manifestations may be restricted to a group of muscles or may involve all voluntary muscles. Likewise, autonomic manifestations may occur during any type of epileptic seizure and sometimes may be implicated in sudden onset death.They can also appear together with other symptoms or signs.

The electrical discharges in the brain affect the sympathetic, parasympathetic and enteric nervous system. The functions affected will be different depending on where the onset of the discharge starts. The activity of the autonomic nervous system (ANS) is an easy non-intrusive way to assess the changes in the brain. By studying the behavioural or physiological changes which result from an abnormal activity of the ANS we can speculate about the epileptic seizure onset zone. The parasympathetic and sympathetic systems control and regulate different functions such as heart rate, perspiration and body temperature, etc. We can measured these biomarkers easily. Nowadays, some of these can be measured simultaneously with EEG monitoring such as the ECG.

Cardiac signals are robust and easy to record. It is reported in the literature that often occur tachycardia phenomenons as a response to sympathetic changes. In spite of bradycardia that can also occur, as a response to parasympathetic changes. In several studies tachycardia was shown to be present in arround 90% of the epileptic seizures [14].

1.2.2 Video-EEG

Video-EEG (VEEG) is known as the most accurate method for monitoring patients who suffer from epilepsy. This method has an high success rate of 80% for the detection and distinction of paroxysmal behaviours[15]. VEEG enables the evaluation of seizure's characteristics, localization of the onset and quantification of the interictal and the ictal epileptic discharges and it also allows the characterization of behavioural changes. Continuous monitoring using a split-screen with Video-EEG enables the correlation of the electrical signal from EEG with the paroxysmal behaviours occurring simultaneously.

In spite of being an expensive and time consuming procedure, the Video-EEG is a method with an high value for the diagnosis and characterization of the disease. In fact, it is the gold standard method. While the technician is watching the video he can mark the onset of the changes in the patient's behaviour. After that, when the EEG signal is analysed, the EEG onset is also marked where there are changes in signal. By observing the signal from all electrodes placed in diferent positions on the scalp, the origin of the electrical discharge may be extrapolated as well as when it has started and how it is spreading. This is possible because when an alteration in electric signal is observed, information about the onset time and about the electrode in which the first change was detected is available. Information coming from the other electrodes in which alterations occur after the first one complement the data, thereby enabling the analysis of these all informations.

In VEEG the temporal marks of the onset of the seizure and clinical manifestations over the EEG monitorization records are made manually after the records are acquired and the entire record is checked-up looking for clinical and/or electroencephalography seizures.This is a time-consuming task.

Despite all the advantages and high accuracy of VEEG, it is a relatively expensive monitoring method, time consuming and it is limited to usage in a hospital environment. There are many associated costs such as standard hospital costs, equipment, technicians, doctors and nurses' time.

According to Ghougassian et al. [16], a lot of studies have been made in order to examine the sen-

sitivity and specificity of VEEG and all of them achieved an high correlation. They noted a high accuracy on non-epileptic seizures detection, which sometimes are misunderstood with epileptic seizures.

1.2.3 Actigraphy in brain disorders

Actigraphy is a non-invasive method of measuring movement. It is an accelerometer usually worn on the wrist that records movements for a long period of time. The functioning principles of accelerometers will be discussed throughout the next chapters. Actigraphy has been used in many medical applications ranging from sleep disorders to detecting changes in physiological variables and others. This technique is useful in medical applications with the purpose to determine changes in frequency or amplitude on limbs motion. Nowadays, accelerometers are already used together with EEG, EMG and ECG during polysomnography monitoring in order to study sleep diseases[17]. In addition, accelerometers are also able to help in the evaluation of tremors Parkinson's disease , and in therapy for patients with cerebral palsy[18].

Some studies have been made in order to detect epileptic seizures with the help of actigraphy.

Table 1.1: Three studies perfomed about detection of epileptic seizures in patients by means of accelerometry.

Article	Sensor	Sensivity	General description	Validation Method
Measurement and quantification of generalized tonic-clonic seizures in epilepsy patients by means of accelerometry - An explorative study [19]	ADXL330 Three-dimensional accelerometer	100%	Motion data acquisition system with a display analysis system/algorithm for continuous analysis of acceleration signals. Send data to a notebook located near the patient. Non-intrusive method.	VEEG
Detection of seizure-like movements using a wrist accelerometer [20]	Three-dimensional accelerometer	Adjustable 1-100%	Smart-watch which detects rhythmic, repetitive movements of an extremity and sends a signal via bluetooth to a computer, alarm device and logs the complete event data. Non-intrusive method.	VEEG
Long-term home monitoring of hypermotor seizures by patient-worn accelerometers [21]	Three-dimensional accelerometer	95.71%	System with four Three-axis accelerometers. ACM signals are recorded synchronously with standard VEEG recordings.	VEEG

Table 1.2: Three studies performed about detection of epileptic seizures in patients by means accelerometer signals - continuation.

Article	Clinical Limitations	Type of seizures detected	Success cases (%)	Aim	Place & Time monitoring
Measurement and quantification of generalized tonic-clonic seizures in epilepsy patients by means of accelerometer signals - An exploratory study [19]	Synchronization is done separately from the EEG equipment. It is checked twice a day by staff. Seizures are detected only inpatients with a specific type of epilepsy.	GTCS	$\geq$ 75 %	Design and validation of an ACM-based detection system for GTCS detection in real-time.	Forearm. Long-term home monitoring.
Detection of seizure-like movements using a wrist accelerometer [20]	Non-synchronized with EEG signals. Data is reviewed separately and then correlated. Seizures are detected only inpatients with a specific type of epilepsy.	GTCS and partial seizures.	$\geq$ 50%	Validate a wrist-worn motion detector to detect tonic-clonic seizures.	Wrist. Ambulatory.
Long-term home monitoring of hyper-motor seizures by patient-worn accelerometers [21]	Seizures are detected only in patients with a specific type of epilepsy.	GTCS	57.84%	Comparison between VEEG-based seizure detection and ACM data	Two wrists and two ankles. Long-term home monitoring.

In the tables above, table 1.1 and table 1.2, a comparison between three studies on the validation of three different motion detectors was made. All of them have an high sensitivity to detect generalized tonic-clonic seizures, which represent the most striking of seizures. An accelerometer device is able to measure translational accelerations. As refered above the gold standard method for the diagnosis of epilepsy is long Video-EEG monitoring. However, this is an intrusive method. Furthermore, it requires the patient staying in an hospital environment during the exam. Thus, it can not detect seizures outside the hospital.

As we know from literature [22], some epileptic seizures may include uncontrolled movements of

the arms or even legs, depending on the type of epilepsy. Thus, these movements can easily visible in accelerometers signals. The combination between the video-EEG and this device can hypothetically have a very high precision to identify seizures. Moreover, the detection method using accelerometers is a low cost and strictly non intrusive for the patient. Another advantage is that this device can provide home monitoring for a long term, while VEEG can only be acquired in hospital environment and it is also more expensive.

Actigraphy can detect abnormalities in the circadian cycle and sleep disorders which can adversely affect epilepsy [23]. Since the relation between sleep and epilepsy is bidirectional because seizures disturb sleep and sleep disorders have bad effects on seizure control, actigraphy can eventually be an important tool to diagnosis sleep disorders in patients with epilepsy. It is therefore of crucial importance to prove the relation between the data from actigraphy and the data from video-EEG. Some studies were made to validate this correlation and some of them are described in tables above. Another study was made to validate and assess the use of actigraphy as a tool in studying sleep patterns in children with epilepsy[24]. It had an high correlation found on actigraphy data, saying that more than 90% of the epileptic seizures had motor behaviour in children and it proves that actigraphy is a good tool for analysing sleep-wake patterns in patients with epilepsy.

1.3 Original contributions

The accomplishment of this work required a multi-disciplinary approach. It was made a particular effort to support the development of this device and algorithms performed with epilepsy studies that have already been developed. The main contributions of this thesis are the following:

- a new device with a small, low-power, 3-axis accelerometer sensor connected through the EEG equipment. This device is placed on the patient wrist and it is capable of detecting movements in a non intrusive way.
- an algorithm to movement detection which will reduce the time consuming work of locating seizures in EEG recordings.
- an algorithm to detect seizures onset which manifest themselves by involuntary movements or activity arrest.

- validation of the method based on data already analysed by the doctors proving the feasibility of using the data to detect the seizure onset.

1.4 Thesis outline

Apart from the introduction chapter, on which the state of the art is presented, the thesis is divided in five chapters. Chapter 2 consists in a description of epileptic seizures and epilepsy syndromes, the classification methods, the treatments available and its impact in patients life. In addition, it is described the gold standard method to monitoring epilepsy, electroencephalography, commonly referred as EEG.

Since the sensor which was used is based on CMOS-MEMS technology, in chapter 3 MEMS technology (micro-electromechanical systems) is described as well as CMOS technology (complementary metal oxide semiconductor). Furthermore, it is presented the operating mode of a typical MEM-accelerometer. Finally, it will be described the accelerometer designed explaining his operation mode and the experimental setup performed for this study.

In chapter 4 experimental results are presented. Firstly, noise filtering was done by estimating the noise through processing signal methods. Secondly, the data was validated through a correlation method related with the data from a commercial accelerometer. After that, it was developed an algorithm to movement detection. Finally, the ACM data were correlated with the signals from EEG in order to validate them to identify a seizure onset. In this chapter all methods are presented and discussed.

In chapter 5 the experimental results are assessed and on this basis future work is discussed.

2

Theoretical framework

Contents

As mentioned in the last chapter, epilepsy is one of the most common neurological disorders worldwide. It affects 50 million people worldwide[25]. Epilepsy is a chronic neurological disease which results from an abnormal and synchronous electrical neuronal activity in the brain. For an appropriate treatment, a correct classification of epileptic seizures and epilepsy syndrome must be done. In this chapter, a definition of epilepsy and epileptic seizures, the classification method and some treatments available are presented. Likewise, the impact of epilepsy in patient life will be referred. Moreover, the gold standard method to monitoring patients with epilepsy is EEG. So, the detailed functioning method of this tool, the engineering principles and the acquisition methods which it is based will be described.

2.1 Definition of epilepsy and epileptic seizure

Epilepsy is a disease which is characterized by a longstanding predisposition to generate epileptic seizures and by the other consequences related with this condition, such as cognitive, psychological and social impairment. It envolves recurrent unprovoked seizures.

An epileptic seizure is a transient occurence of signs or symptoms due to abnormal neuronal activity in the brain. Epileptic seizures may be focal, if they begin in a localized area in one of the brain's hemispheres, or generalized if the onset involves both hemispheres. Seizures manifest themselves according to what function of the cortex is affected, and how the discharge spreads within the brain.

Epileptogenesis is a gradual proccess by which the brain develops epilepsy. Figure 2.1 illustrates focal epileptogenesis, a process that contains multiple steps. An initial injury that can result from many possible causes, may develop into a first seizure. The "latent phase" or "latent period" between brain injury and clinical epilepsy is widely recognised to be a seizure-free, pre-epileptic state during which several molecular events and structural changes gradually mediate the process of epileptogenesis. This concept of "latent period" implies that epilepsy is not an immediate consequence of brain injury[26]. During each step of this process, the different causes of epilepsy may lead to different injuries in the brain affecting different parts of the brain, which in turn implies different manifestations of the seizures.

Research clearly shows the increased incidence and prevalence of epileptic seizures according to age[27]. The prevalence of epilepsy may be a result of other factors like brain tumour, trauma,

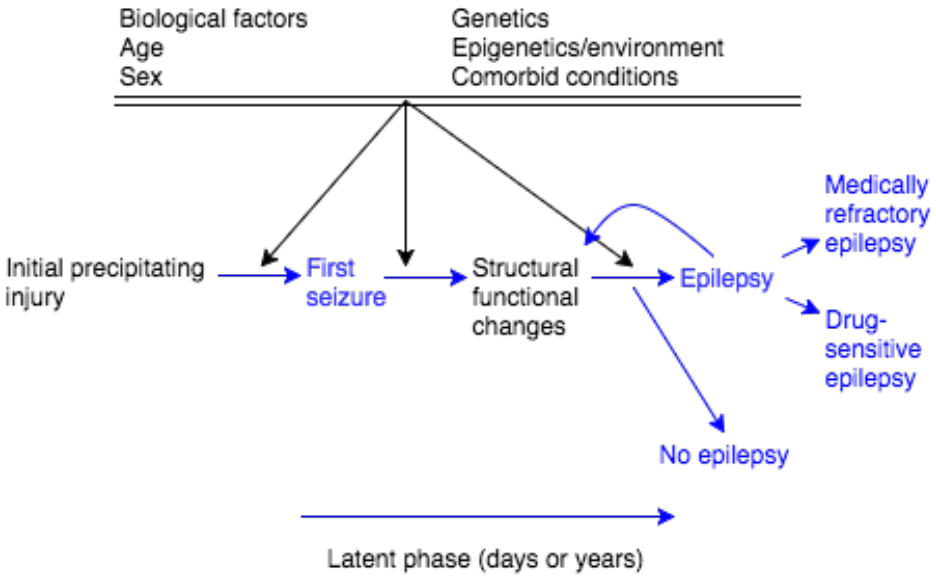

Figure 2.1: Process of epileptogenesis

infection or developmental disabilities. However, in most part of the cases, epilepsy has an unknown origin[28].

2.2 Classification of epileptic seizures and epilepsy syndromes

The first step in the management of an epileptic patient is the correct classification of the seizure type and epilepsy syndrome (because epilepsy is a disorder defined by a particular group of features that usually occur together). According to the cause, the location in the brain as we can see in figure 2.2, and the intensity of neuronal electric discharges, seizures can take very different forms and many different clinical signs may be present.

Nowadays, there are two classifications systems: *The International Classification of Epileptic Seizures* and *The International Classification of Epilepsies and Epileptic Syndromes*.

Partial seizures represent the most part of epilepsy cases [1] and they can be subdivided in two types:

- *Simple partial seizures* are characterized by no loss of consciousness. During simple partial seizures patients have symptoms such as motor symptoms, sensory symptoms (which can be visual, auditory, olfactory, gustatory or even vertiginous), autonomic symptoms (which are described later) and discognitive or physic symptoms.

- *Complex partial seizures* are characterized by loss of consciousness. These seizures may

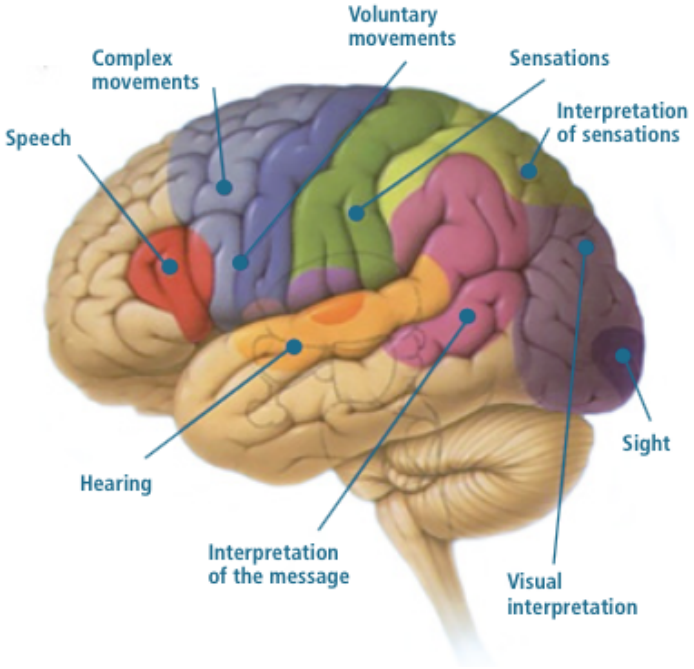

Figure 2.2: Brain topography from [1] page 5

begin as a simple partial seizures and then can be followed by an impairment of consciousness, or the loss of consciousness may begin before. These seizures may occur associated with automatisms like simple gestures or complex gestures, wandering and verbal automatisms.

Partial seizures may or may not be followed by a generalized seizure. Widespread brain damage lead to generalized seizures and it is presumed that the major cause is genetic damage.[29] Both partial and generalized seizures affect autonomic function during ictal, posictal and interictal states.

Epilepsy syndromes are divided according to several features such as etiology, interictal deficits, seizure type, age of the onset and findings in EEG and neuroimaging. These are syndromes with focal seizures, syndromes with generalized seizures, undetermined syndromes or special syndromes [11]. In addition, epilepsy can be classified by aetiology as represented in figure 2.3 and described below. As may be seen in figure 2.3 most of the patients with epilepsy have *Idiopathic/cryptogenic syndromes*.

- *Idiopathic syndromes* means there is no apparent cause and it is presumed a genetic etiology. In this case, epilepsy is a direct consequence of a genetic mutation which determine an abnormality of electrical neuronal activity.

- *Symptomatic epilepsies* which means they have a clearly identified cause. This cause may be

a tumour, a stroke or other brain abnormality.

- *Cryptogenic epilepsies* means that an etiology is suspected, but the exact cause cannot be determined.

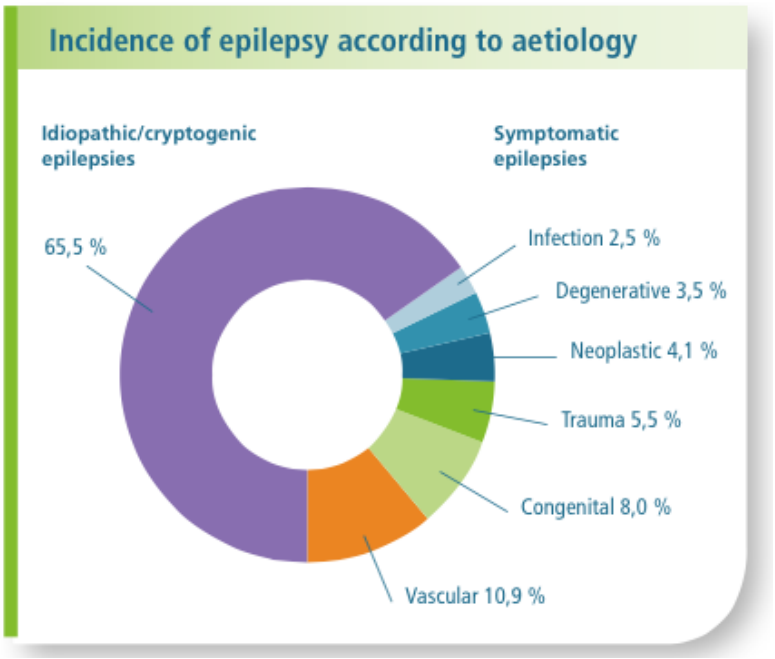

Figure 2.3: Incidence of epilepsy according to aetiology from *Epilepsia. 1993 May-Jun; 34(3):453-68. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Hauser WA, Annegers JF, Kuraldn LT*

Throughout recent years, a new diagnostic scheme for patients with epilepsy was proposed. This takes in account five parameters: ictal phenomenology, seizure type, epilepsy syndrome, etiology and impairment [11].

As stated above, a correct diagnosis is the first step for a correct treatment. With this purpose, doctors start by identifying the semiology of the seizures which process is described below. After a correct classification and identifying the seizures semiology, the most appropriate treatment is chosen.

2.2.1 Seizure Semiology

The precise localization of the epileptogenic zone is crucial for a correct choice of the treatment, especially in the cases when epilepsy surgery is a possibility. The epileptogenic zone is defined as the area of the brain to be removed so that the patient have no seizures after the surgery. It involves the ictal onset zone where the seizures start in EEG. Thus, this area of the brain must be removed for a complete abolition of the seizures[30]. Seizure semiology is an effective tool that enables locating

the symptomatogenic zone which normally is near to the epileptogenic zone. This tool consists in analysing the symptoms and signs during a seizure.

Epileptic paroxysmal events may manifest themselves in different ways. Depending on where the onset location is, the discharge may lead to visual, abdominal, autonomic, auditory, olfactory, gustatory or psychic auras[31].

Epileptic seizures are characterized based on the type of behaviour and brain activity.

- **Autonomic seizures** are epileptic seizures in which the main symptoms of disease are autonomic alterations which manifest themselves as tachycardia, bradycardia or ictal vomiting. Tachycardia and bradycardia are the increase or decrease the heart beat. Tachycardia often precede ictal EEG changes if the seizure onset is in the right hemisphere of the brain. Seizures in the left hemisphere of the brain are often more related with bradycardia[32]. Changes in cardiac signals may provide an easiest way to identify where was the ictal onset in some patients, thereby it can be a potencial biomarker. If the epileptic discharge spreads throughout the right side of the brain, the reponse will be sympathetic and the heart rate will increase. In contrast, if it spreads throughtout the left side, the response will be parasympathetic and the heart rate will decrease [32][14].

- **Dialeptic seizures** are seizures in which the predominant symptomatology is a consciousness disturbance.These consists on episodes of unresponsiveness or decrease responsiveness and moreover they are associated with complete or partial amnesia for the episode [33].

- **Motor seizures** are an important focus in this study. Two motor symptoms (simple or complex) can be seen in patients with epilepsy. First of all, these symptoms may be elementary motor symptoms which are characterized by simple movements, such as clonus or tonic posturing. Simple motor seizures include *myoclonic seizures* which are short muscle contractions and are often present in genelarized seizures, *tonic seizures* which consist of continuous muscles contractions and it can maniffest itself in patients with focal or generalized epilepsies, *epileptic spasms* which is usually used to identify muscle contractions of relatively symmetric and finally, *versive seizures* which manifest themselves as a forced and involuntary turning of the head and eyes in one direction with neck extension associated [31]. Secondly, they may be complex motor symptoms which include automatisms and complex postures. Automatisms are cordi-

nated motor movements which involve muscles activity. Electromiography is used to measure the muscles activity. In current case study, motor seizures will be studied deeply, once we want use an actigraph to measure motor movements during seizures and relate them with the onset of the seizure.

In order to precisely localize the epileptogenic zone, different exams are performed. These exams include Magnetic resonance image (MRI), video and EEG and a correct semiology characterization and all must indicate the same epileptogenic zone. If the results are not in line, the location of the epileptogenic zone is inconclusive, and in that case an almost definitive solution, like surgery, is discarded. Seizures semiology is a subjective tool especially because the same symptomatogenic zone can be activated with a discharge from different epileptogenic zones and moreover this tool does not always allow an accurate differentiation between focal and generalized epilepsy.

2.2.2 Autonomic nervous system in patients with epilepsy

All autonomic functions can be affected during a seizure, including parasympathetic and sympathetic systems. Seizures usually activate sympathetic nervous activity and thereby changing the heart rate and blood pressure. On the other hand, the activation of parasympathetic or the inhibition of sympathetic may predominate in partial seizures [34]. The autonomic nervous system and his functioning method assume an important knowledge in this work. This is because through that we may assess the changes that occur during a seizure. In the autonomic nervous system, there are parallel chains which connect the central nervous system and the effector cells. These parallel chains are constituted by two neurons and the synapse between them is in a cell cluster called *autonomic ganglion*, outside the central nervous system[2].

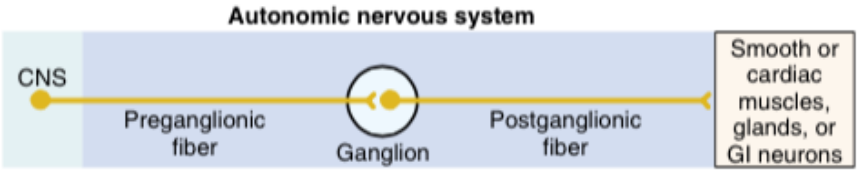

Figure 2.4: Overall plan of the autonomic nervous system from [2] page 217

As can be seen in figure 2.4 the nerve fibbers between the central nervous system and the ganglion are called *Preganglionic fibber* and those passing through the *ganglion* and then the *postgan-*

glionic fibber connects the effector cells and the *ganglion*.

The autonomic nervous system (ANS) are subdivided into **sympathetic** and **parasympathetic** components due the anatomical and physiological differences within ANS. The nerve fibbers of the sympathetic and parasympathetic components leave the central nervous system at different levels. The anatomical arrangements in sympathetic nervous system act all together as a single unit, therefore, some small segments act independently. On the other hand, the parasympathetic nervous system is made up of components which act relatively independently.

Both autonomic nervous system and somatic nervous system are part of peripheral nervous system. Nerve fibbers, which are called just nerves, connect the central nervous system with all receptors and effectors in all parts of the body. The difference between somatic nervous system and autonomic nervous system is that the neurons of the somatic innervate skeletal muscle, while the autonomic neurons innervate cardiac muscle, glands and neurons in gastrointestinal tract.

We can assess to autonomic nervous system, for example, through the heart rate (HR) or blood pressure (BP) . Several studies proved that partial and generalized seizures are associated with a set of changes in heart rate, blood pressure, respiratory patterns, pupillary size, vasomotor and sudomotor activity and others, affecting the sympathetic and parasympathetic nervous system [34]. These autonomic effects of seizures may result from the stimulation from limbic to hypothalamic areas. It was proved that epileptic discharges from limbic structures are deeply connected with hypothalamic regions, which may change autonomic functions between and during the seizures.

Relation between seizures and autonomic nervous system (ANS) is very important and complex. An epileptic seizure is defined as an abnormal neuronal electrical activity of the brain which can involve centres of regulation of autonomic activity. Autonomic symptoms may be present during, before and aftermath the seizure and its propagation.

An electrical discharge in the brain, which results from an epileptic seizure, spreads throughout a probable path as we can see in the figure 2.5.

The ictal impulse may imply Temporal lobe, frontal lobe or both. The insular cortex is involved in both temporal and frontal seizures, and Hippocampus is involved only in temporal seizures. After that, this activity spreads through the limbic system involving the amygdala, hypothalamus and thalamus.[35] These will stimulate the ANS nuclei in medulla, including the nucleus tractus solitarius

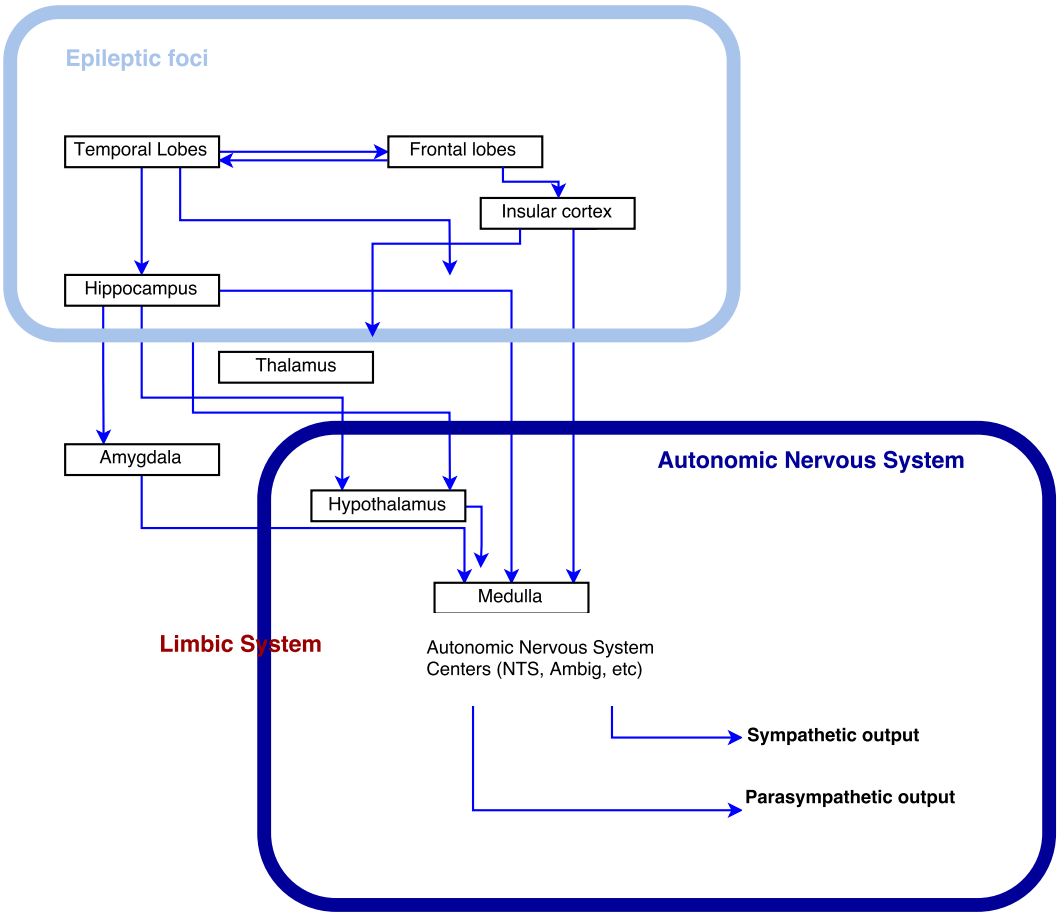

Figure 2.5: Probable paths of propagation of the epileptic electrical activity to the limbic system and autonomic nuclei

(NTS) and ambiguus nuclei. Finally, the efferent discharges will be generated in both sympathetic and parasympathetic components.

2.2.3 Treatment of epilepsy

The aim of treatment is to provide the patients with a normal lifestyle, ideally free of seizures. In the majority of patients, anti-epileptic drugs are prescribed with the purpose of minimising the occurrence of the seizures. However, it is important to be aware of the response to anti-epileptic drugs by the patient. Since some of them may resist to the drugs, a long-term prognosis have to be done.

The anti-epileptic drugs are chosen based on the patient gender or age, on the type of seizures (whether there have been recurrent seizures or if it is an isolated case and also if the seizures have had a partial or generalised onset). After taking all of these factors into consideration, a drug is chosen more efficiently. The aim of treatment is to stop the seizures without side effects or at least reduce them. In order to choose the correct treatment, the patient must go through three steps. Firstly a

drug is introduced with a careful increase. Secondly, whether the seizures continue, the dose should be increased to the maximum quantity which is tolerated and then change the medicine in the case the benefits of the drug does not compensate the side effects. Finally, if the seizures don't stop, a combination of two or more drugs should be done[36].

In some patients a surgical intervention can be considered. The resective surgery is limited to those having an 80% of success rate against low rates of mortality or permanent neurological deficit[36]. An higher success rate is achieved with an higher accordance about the localization of the epileptogenic zone in the pre-surgical evaluation. Although, there are about 30% [28] [36] of patients with epilepsy syndrome who are resistant to anti-epileptic drugs and surgical treatments.

However, there is an alternative to bad-candidates for resective epilepsy surgery. In patients with drug resistant epilepsy, a vagal nerve stimulation (VNS) or deep brain stimulation (DBS) can be done. To accomplish this, a surgery must be performed in order to implant a stimulator in the neck on the left side of the vagus nerve[37]. The VNS directly affects the frequency of the seizures, however, it may take some time until a satisfactory safety profile is achieved. DBS consists in a bilateral stimulation of the anterior nucleus of the thalamus (ANT) by the implantation of two electrodes in this region resulting in improved seizure control in humans[38].

2.3 Impact of epilepsy

People suffering from epilepsy can carry out all normal activities and have a normal professional life. However, they must be careful with some things: drinking alcohol, fever, certain medicines that stimulate the activity of central nervous system, flashing lights, etc.

Some symptoms could be related to epileptic seizures. These could be a consequence from seizures or anything else that may cause the epilepsy or could be related, for example, with the side effects of medicines. Moreover, epileptic seizures may lead to changes in autonomic systems and thus could affect the sympathetic, parasympathetic and whole nervous system. A brief explanation of the functioning of these systems will be presented later.

In addition to having seizures and apart from all damages that it represents on the instant that it happens, the impact of epilepsy includes mood and behaviour disturbances and a decrease of quality of life for the patients and for their family.

Depending on the seizure onset location and also on whether it is focal or generalized, some behavioural functions or physiological functions may be altered. The impact of epileptic seizures when these happen on a long term, can result in irreversible consequences for the patients health, including anxiety, memory and cognitive impairments, high blood pressure, changes in heart rate, obesity, psychiatric problems, among others.

2.4 Clinical Electroencephalography

Electroencephalography (EEG) is a diagnostic clinical tool for assessing brain activity. EEG is traditionally interpreted by visual analysis of the signal traces, associating defined features of EEG, such as the structure and symmetry of important spontaneous oscillations, relative frequencies and their spacial organization and the presence of paroxysmal waveforms which represent epileptic discharges, with particular brain states. In recent years, clinicians have learned to use these EEG features as a powerful tool to identify focal or widespread cortical abnormalities. The EEG results from currents flowing in and out of the cells. Ions flow in and out of cells creating ionic flow also in cellular space. Actually, there are some small currents associated with proteins that work to restore ion balances, and are thereby working against the electrochemical gradient, such as Na^+, K^+, Ca^{2+} and H^+. These flow currents follow Ohm's Law, that can be written in the form:

$$I = \frac{V}{R} \tag{2.1}$$

If we refer the cell membrane currents as conductance and considering that resistance is its reciprocal, the current may be expressed as:

$$I = g(E_m - E_{rev}) \tag{2.2}$$

In equation 2.2 E_m is the membrane potential and E_{rev} is the reversal potential which is dependent on a set of the concentrations inside and outside the cell. EEG records cerebral signals which contain overlapped oscillations in a large range of frequencies. In humans, this range is recorded from 0.05Hz to 600 Hz [1].Furthermore, the signal recorded may have some interference from extracerebral electrical sources, for example from muscles activity, as well as some attenuation. The electrical signals recorded in EEG are the electrical value in volts (of the order of mV) for the flow of

ions throughout the brain.

The main pathology in EEG findings from a patient with epilepsy is a spike, a transient, high amplitude deflection in the local field potential (typically of the order of hundred micro volts). After the spike of electric neuronal activity may be identified an amplitude attenuation with little activity. So the interictal discharges often occur as isolated events, while the discharges that result from a seizure appear in rhythmic trains.

The physiology requires a different sensor to record the different types of activity over the brain. We can use microelectrodes for cellular events, mini electrodes to record from cortical columns, intracranial electrodes to record from individual gyri and scalp electrodes to record from large cortical areas. In the present study, it was performed a long-term monitoring in patients through video-EEG with scalp electrodes.

2.4.1 Engineering principles

The instrument, which we use to measure the voltage, should ideally not disrupt the regular performance of the circuit. Nowadays, in clinical environment an EEG machine is used to measure the electrical signals from the brain discharges. The main aim of this measuring is that the measured voltage most accurately reflect the real voltage from the discharges. In order to achieve this aim the input resistance of the EEG machine should be much larger than the resistance of the source, which normally may be measured on the electrodes. The electrode resistance is typically on the order of less than $5k\Omega$ [1] and in the most clinical EEG equipment the input impedance is $100M\Omega$ or $200M\Omega$ for higher electrodes impedance [39]. It is always needed to check the skin-contact impedance.

Some recordings of EEG signals requires amplifying the signals. EEG voltages are measured at each electrode relative to some chosen reference electrode. To measure these voltages a specific 18 kind of amplifier is employed, an instrumentation amplifier.

As we may see in figure 2.6 the output voltage is proportional to the difference between the two input voltages, thereby measuring the potential difference between the electrode and the reference. The general expression for a differencial amplifier is:

$$V_{out} = A_d \times (V_+ - V_-) + A_{cm} \times \frac{1}{2}(V_+ + V_-) \tag{2.3}$$

In equation 2.3 the differential gain is A_d and the common-mode gain is A_{cm}. A good differential

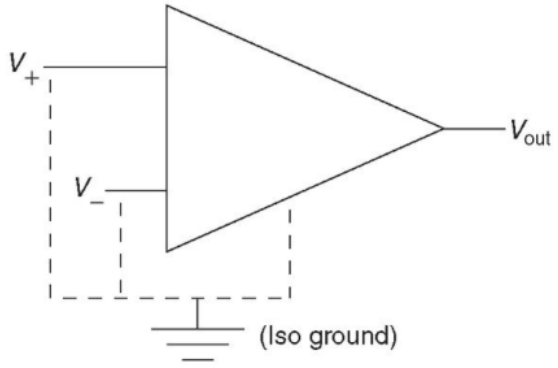

Figure 2.6: Simple concept of a differential amplifier [1].

amplifier has a large A_d, and it also has as small A_{cm} as possible. The CMRR (common-mode rejection ratio) is a measure for how well this amplifier rejects the average voltage. It is typically expressed in the logarithmic decibel scale. In our equipment the CMRR of the EEG input is 105dB or greater and in the bipolar input is 100dB or greater [39]. For a good differential amplifier we may know that Common-mode rejection ratio (CMRR) must be at least 80dB, in order to the ratio of the differential gain and the common-mode gain be 4 orders of magnitude.

In addition the lowpass, highpass and notch filters are very important for EEG recordings. In modern EEG equipments, the lowpass, highpass and notch filtering are handled by digital processing. The concepts of lowpass and highpass filters can be combined to create bandpass filters. This enables to acquire signals with frequency components only over a limited range bordered by the high and low pass filters, thereby attenuating the very low and very high frequencies. The notch is a bandstop filter which is used to eliminate the powerline noise (the most common interferencies from outside sources are voltage sources which operate at 240V, 50Hz).

The EEG equipment is basically an ADC (analog digital conversor), which converts the electrical signals from the biological system (analog signal) to digital representation. The digitisation of the signal quantise along two dimensions: time and magnitude, which means that samples are acquired at discrete and regular time intervals and converted to discrete magnitude values. The sampling rate is always the same whether the magnitude of the input signal changes slowly or quickly over time. The right choice of sampling rate is very important because it restricts the information available in digitised series. The sampling frequency (f_s) must satisfy the condition of the Nyquist sampling theorem, which states that a continuous time signal can be represented by a set of samples, provided

that the number of samples in each unit of time is at least double of the maximum frequency in the signal. This theorem can be represented by the equation below [3]:

$$F_s \geq 2 \times f_{MAX} \tag{2.4}$$

In equation 2.4 f_{MAX} is the limit of frequency from which the spectral density of power is not significant. If $f_s > 2f_{MAX}$ the additional frequency components can easily be filtered by a lowpass filter with a bandwidth from 0 to f_{MAX}, thereby reconstructing the original signal.

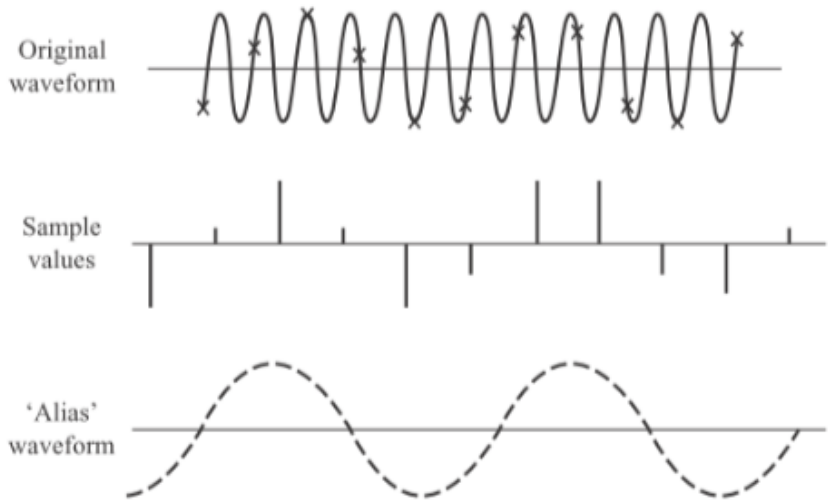

Figure 2.7: Aliasing consequence. [3].

If the frequency chosen is too small the sampling process may have consequences, which are represented in figure 2.7. As can be seen above in the figure, the signal reconstruction can be a sinusoidal wave with a very different frequency when compared with the original wave. This effect is known as aliasing. To avoid the aliasing of noise above the Nyquist frequency limit, ADCs have an analog filter prior to the digitisation step, called antialisasing filter.

Another important characteristic of an ADC is the signal resolution. The resolution of the analog to digital conversion is limited. The ADC used in this study has 16 bits. With 16 bits, there are 65536 distinct possible values ($2^{16} = 65536$). The number of bits to store each sample value is called bit-depth. There is a easy relation between resolution, bit depht and the range (which is the maximum voltage recorded) and that relation is represented in the equation 2.5.

$$Resolution = \frac{Range}{2^{bitdepth} - 1} \tag{2.5}$$

For current EEG equipments, a typical dynamic range is from -5 to 5 mV. With a bitdepth equal to 16 bits, the resolution is:

$$\frac{5,000 - (-5,000)\mu V}{2^{16} - 1} = \frac{10,000\mu V}{65535} = 0,153\mu V \tag{2.6}$$

2.4.2 EEG acquisition

As already mentioned above, the current passing through an electronic machine is simply electrons flowing through metal conductors. In biologic systems, there are no free electrons. Instead, the flow of charges is composed by positively charged sodium cations (Na^+) and negatively charged chloride anions (Cl^-). Thus, chemical reactions occur, where electrons are transferred between the biological system and electrodes. For example, if the flow of charges from a biologic system to electronic system is negative, an electron will be transferred from Cl^- to a platinum electrode. The electrodes material should not interact chemically with the electrolytes of the scalp, those include gold, silver chloride, tin or platinum.

Electrodes are composed by a conductor added to a wire that may be connected into the input of the recording machine. The current carries positive ions to the negative part of the junction and inversely. Consequently, the electrode will be polarized. Furthermore it favours the current flow in one direction and an opposes current flow in the opposite direction. The polarization of the electrodes can lead to some distortions in the recordings. This effect can me minimized taking a few precautions.

In the current study we only use data from patients with monitoring made with scalp electrodes, which are represented in figure 2.8 with the letter B.

Each scalp electrode is applied in a precise scalp location after preparing the scalp to reduce the electrical impedance. The electrode resistance should be between 100Ω and 5000Ω , according with the international standards for the EEG. In this study, it has been used a specific system of electrode placement that was proposed by the American Electroencephalographic Society - ACNS in 1991 as can be seen in figure 2.9 [1].

However, the most recommendable combination has at least 21 electrodes from the international 10-20 system. The anatomical location of the electrodes are designated by letters and odd-numbers

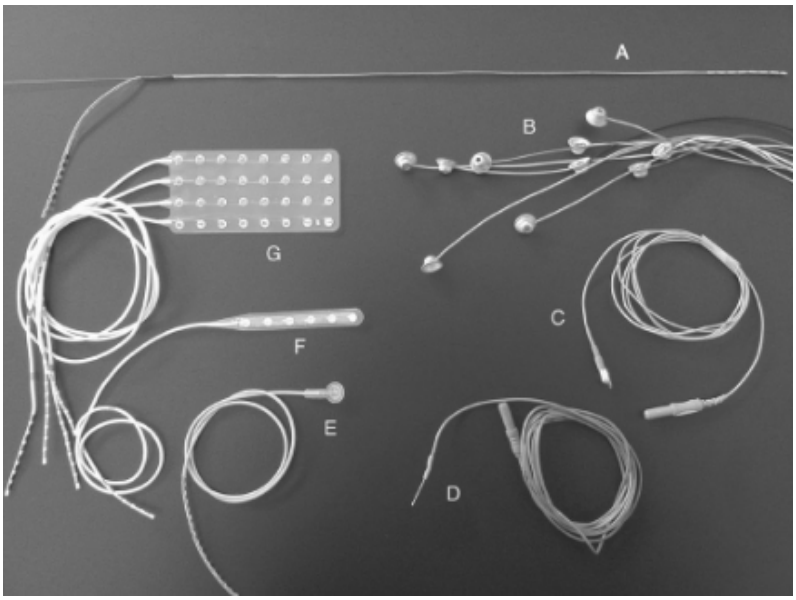

Figure 2.8: The most common electroencephalographic electrodes[3].

if the electrodes are placed over the left side of the head or even-numbers whether the electrodes are placed over the right side. The approximate anatomical location are designed by letters ("F" for frontal, "Fp" for front temporal, "C" for central, "T" for temporal, "P" for parietal, "O" for occipital and "z" indicate zero).

The system combination in figure 2.9 was designed for placing 75 electrodes over scalp locations.

The voltage at any point is measured with respect to another point. There is not an absolute value, it always is a difference between two points. In electronic circuits this reference is typically the ground. However, in EEG, the voltage on scalp is measured with respect to another point on the scalp or at least the body. In the current study, two types of setups have been used: bipolar and referential. In a referential montage, the voltage at each electrode is measured with respect to a common reference. Ideally, the common reference electrode has not any activity with respect to the activity of interest. It is usually used some reference electrodes which is A1 and A2 (both placed on the ear in opposite sides), A1+A2 (both linked), Cz (placed on the neck-chest) and finally the average reference. The average reference is derived by averaging the voltage in all active electrodes and it must exclude artifacts from the calculation of the average reference, avoiding the contamination of the reference electrode by electrode polarization and drift. In bipolar setups, both electrodes are connected as an active electrode, thus there is no a common reference. A channel involving these two inputs will be a difference between the active input minus the reference. The actigraph will be connected through

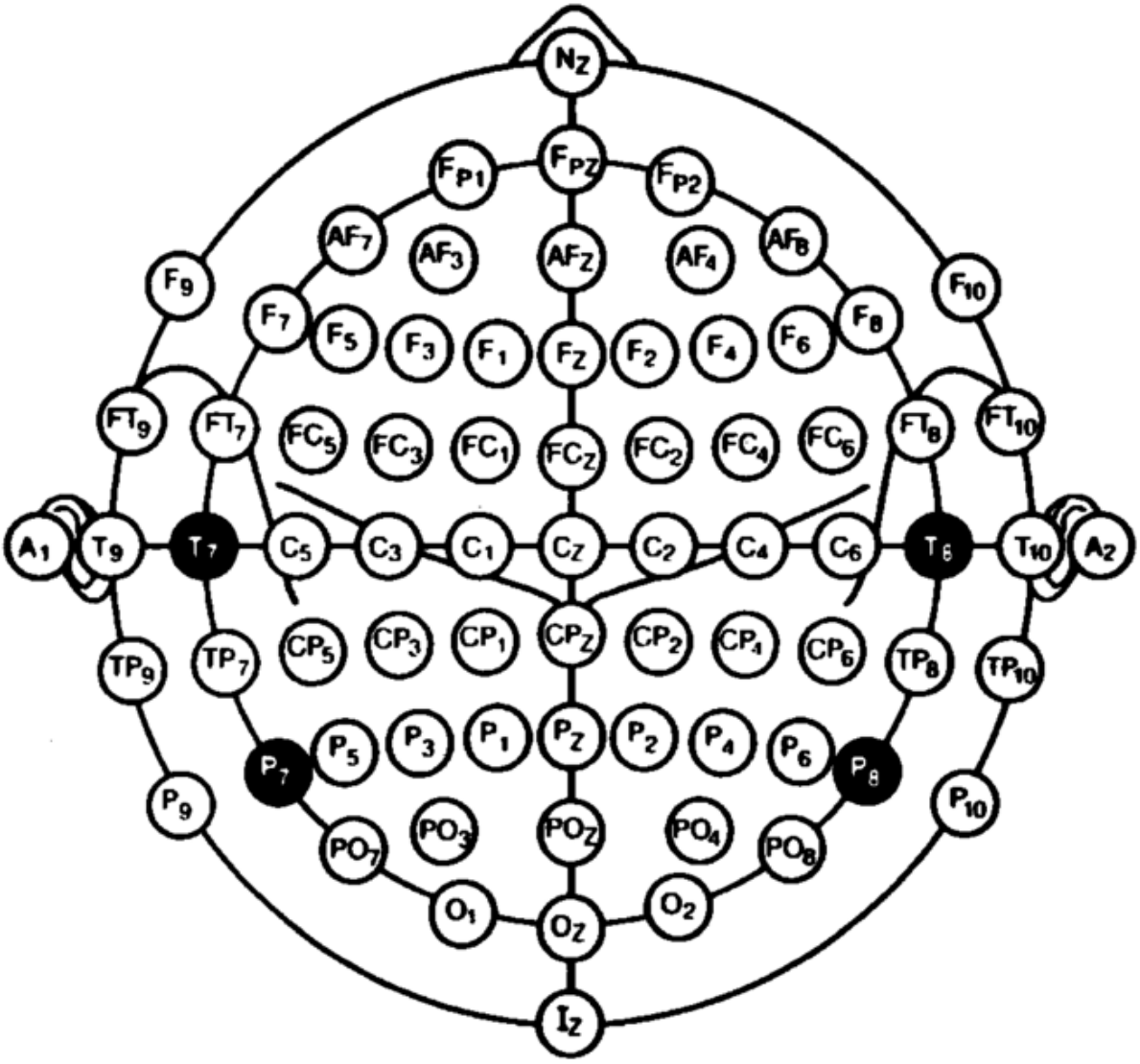

Figure 2.9: Modified combination nomenclature (Copyright 1990 American Electroencephalography Society).

a bipolar channel, where the active channel will be the axis over that there is movement and the reference will be the ground (i.e. 0V).

2.4.3 Recording non-cerebral potentials

Some non-cerebral potentials are recorded in EEG equipment in patients with epilepsy. An epileptic discharge may affect some other functions from the normal functions of the human body.

- Eye movements are often recorded in EEG monitoring, once those movements can be helpful to distinguish from the possible similarities between frontal and anterior temporal cerebral potentials. Eye movements are usually recorded through two channels (E1 and E2). Both channels are referenced to a common reference placed in the ear (A2). This arrangement allows to

distinguish between horizontal and vertical eye movements. Eye movement monitoring is also used to detect REM (Rapid eye movements) sleep, which is a phase of sleep characterized by a random movement of the eyes.

- The Heart beat is also recorded during the EEG monitoring. An EEG electrode is placed on the neck or the chest and another one is placed at some distance away in order to record ECG (Electrocardiogram) signals. That is because an epileptic discharge in the brain may increase or decrease the heart rate depending on where was the onset of the discharge.

- Muscles activity is also monitored with EEG electrodes. An electrode is placed a few centimetres below the mouth making records from EMG (electromiography) movements. This electrode will be connected to the EEG equipment referenced to another electrode placed on the neck.

- In the current study we will measure movements of the arms placing an actigraph on the non-dominant wrist. Since some types of epilepsy cause involuntary movements of the arms or legs with some type of pattern if the onset of the epileptic discharge was in specific parts of the brain.

Finally, a continuous video is recorded over all the time of the monitoring in order to detect some abnormal changes in patient behaviour. At the end, the technician can compare all the features and make a more precise diagnosis.

3

Actigraphy sensor

Contents

An accelerometer is an electromechanical device that is usually used to measure acceleration.

An important concept that we must understand is the concept of acceleration. Assuming **r** the distance vector from some given origin to a particle and **v** its vector velocity:

$$\mathbf{v} = \frac{d\mathbf{r}}{dt} \tag{3.1}$$

Defining the linear momentum **p** of the particle as the product of particle mass and its velocity:

$$\mathbf{p} = m\mathbf{v} \tag{3.2}$$

As a consequence of interactions with external objects or fields, the particle can experience forces of various types. **F** is the vector sum of these forces. According to *Newton's second law of motion*, the motion of the particle in a reference frame is described by:

$$\mathbf{F} = \frac{d\mathbf{p}}{dt} \tag{3.3}$$

and

$$\mathbf{p} = \frac{d}{dt}(m\mathbf{v}) \tag{3.4}$$

As in most of the cases the mass of the particle is constant, equation 3.3 reduces to:

$$\mathbf{a} = \frac{d^2\mathbf{r}}{dt^2} \tag{3.5}$$

Instantaneous acceleration is defined by equation 3.5 [40]. According to the *International System of Units* the acceleration is referred as an *a* and it is measured in meters per second squared (m/s^2) [41].

There are many types of accelerometers reported in literature and they have a lot of different applications.

Most accelerometers are too big and difficult to use in small devices since micro devices use usually microelectronic circuits for their fabrication. Researchers developed a different type of accelerometers smaller than these ones, the MEMS (microelectromechanical systems) accelerometers.

In this chapter, MEMS technology principles are presented as well as a brief explanation of the crystallography of single-crystal Si (Silicon) and a list of its properties are presented in order to classify the importance of Si as a sensor cristal.

3.1 MEMS technology

Micro-electromechanical systems (MEMS) were one of the technological developments during the last decade of the 20th century. MEMS are essentially composed by micro-fabricated mechanical and electrical structures which work together for perception and control since that they may work as sensors and actuators. MEMS lead to a lot of innovation in terms of processes, equipment and materials. Due to its small size and simplicity of operation, MEMS accelerometer sensors are usually used in gaming applications, mobile handsets, and more importantly in this study, on the human body to analyse tremor and other changes in physical activity. [4]

The most notable elements of MEMS are micro sensors and micro actuators which are appropriately characterized as "transducers". In the case of micro sensors, the device converts a measured mechanical signal into an electrical signal. These micro sensors are able to sense several types of measurements including temperature, pressure, inertial forces, chemical species, magnetic fields, radiation, and in the case of the current study the acceleration.

MEMS technology uses techniques of micro-fabrication technology. However, there are some differences between microelectronics circuits and MEMS. For example, while a microelectronic circuit is internally compact and has compact structures, MEMS have holes, cavities, channels, cantilever membranes and so on. In this study, a MEMS sensor based on silicon was used. The focus on MEMS based on silicon is a result of the wide knowledge on silicon material and micro fabrication over the last decades of research.

The use of MEMS technology has many advantages, like the miniaturisation of existing devices and the development of new tools to interact with the micro-world. Miniaturisation brings a decreasing of material consumption which reduce the cost of the devices. It can also increase the applicability of MEMS in places where a traditional system does not fit. Moreover, MEMS can be related with system integration, once the MEMS on silicon may be integrated directly with electronics. Thus, MEMS technology not only make things smaller but often makes them better.[7]

3.1.1 MEMS fabrication

Silicon (Si) wafers are usually used as substrates for bulk machining (which is the process used to produce micro machinery or micro electromechanical systems), since they can be anisotropically wet etched, therefore forming highly regular structures. Instead of dry etching plasmas, this technology uses pools of liquid as tools.

Single-crystal Si is a great substrate choice based on its viability for integrating sensors and electronics on the same substrate, and its intrinsic mechanical stability. Silicon has a high cost per unit area, but, on the other hand, it has a small feature size which allows its implementation in very small devices. The employment of Si has a big advantage that derives from the easy process of accommodation using thin film deposition equipment. It also provides more flexibility in design and manufacturing than others. The major mentioned disadvantage of using Si is usually when the size of the device is not important and there is no need to incorporate electronics in the same substrate and so there is no need for the high cost. In addition, a huge advantage comes from being an easier-to-package substrate.

The etching process involves transport of reactants to the surface, surface reactions and transport of products from the surface. It is inherently an electrochemical process which involves electron transfer processes as part of the surface reactions.

Surface micro machining is a process to build micro structures by deposition and etching of various structural layers on the top of the substrate. Polycrystalline silicon is usually used as one of the layers, since it has a high purity form of silicon commonly used by the electronic industry. An additional silicon layer is added to etch out and create the necessary hole in the thickness direction. This structure will be very oxide thin with a size of a few micrometres. This machining process has a huge advantage allowing to build micro systems in which the electronic and the mechanical components are built in the same substrate. The structures are built on the top of the substrate and not inside it, thus its properties are not important as in bulk machining. Therefore the expensive structures of silicon can be replaced by cheaper substrates.

Bulk micro machining is a process on which micro machinery or micro electromechanical systems are built and where a silicon substrate is selectively etched to produce structures. One of the major classes of bulk micro machining is wet bulk machining (WBM).

WBM is usually done with the help of chemicals. During this process, the silicon substrate is immersed into a solution of reactive chemicals and these etch the exposed regions of substrate at measurable rates. Alkaline liquid solvents are usually used in this process to dissolve silicon which has been left exposed by the photolithography masking step. The dissolution of the silicon with the alkaline solvents is done in a highly anisotropic way. As is referred in literature, some crystallographic orientations are dissolved 1000 times faster than others. [4] [5]

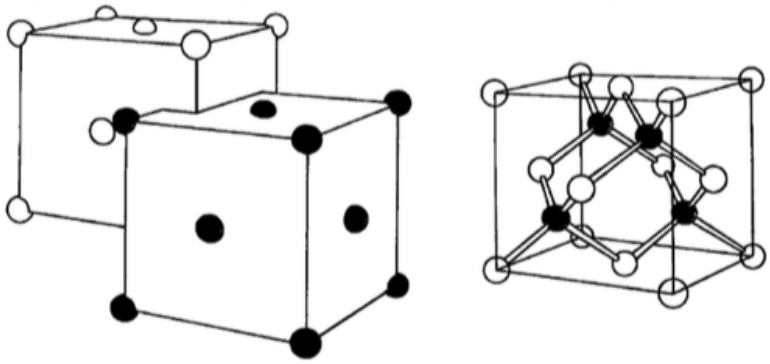

Figure 3.1: The diamond-type lattice of the silicon from two face-centred cubic unit cells. Si forms four covalent bounds making tetrahedrons From [4]

In silicon anisotropic etching the plane [111] is etched at slower rate than all other planes. This is because of the high density of silicon atoms exposed to the etchant solution in this direction as can be seen in figure 3.1 by overlapping the plane [111] shown in figure 3.2.

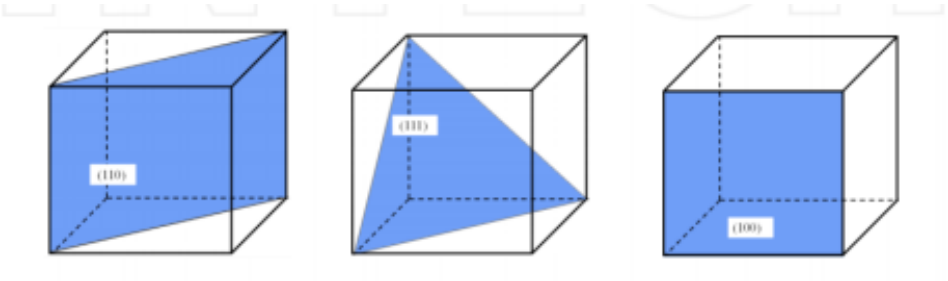

Figure 3.2: The most common orientations used in the integrated circuits [100] [111] and micro machining [110] From [5]

The high etch rate and selectivity of the wet bulk machining technology is a huge advantage for the MEMS industry. The choice of the mask should take into account that it has to dissolve at a much slower rate than the silicon substrate. The etch rate can be modified by the chemical composition of the solution, changing the dopant concentration in the substrate, regulating the temperature of etching or changing crystallographic planes of the substrate. With the purpose of controlling the

etching process and to achieve uniform depths across the substrate, etched stops have been used including dopant etch stops, electromechanical etch stops and also dielectric etch stop.

3.1.2 CMOS-MEMS technology

In order to facilitate the wiring of MEMS structures to integrated circuits CMOS MEMS technology is used. CMOS-MEMS technology is the integration of MEMS technology with the mainstream CMOS technology. To achieve an overall high performance from the devices, the parasitic capacitance is reduced with a monolithic integration of the CMOS-MEMS. Monolithic integration is also known as integration circuit (IC) which is a set of electronic circuits on a small plate (chip), usually silicon. A post-CMOS MEMS technology provides robust and sensitive detecting structures. In this technology, the fabrication of the CMOS circuit is independent from the MEMS structures, which enables integrating on its high performance mechanical structures made of bulk materials with high electronics performance.

The first main integration method for post-CMOS micro machining is to add, on the CMOS substrates, MEMS structures and during which the CMOS layers are being un-etched over all structure micro fabrication. A second method is to build the MEMS structures by performing micro machining straightly in the CMOS thin film substrate or layers.

3.2 MEMS accelerometers

Firstly, it is important to define what an accelerometer is and how it works. Acceleration is measured due to the phenomenon of weight by an object related with a frame of reference of the accelerometer. There are many types of accelerometers reported in literature [42]. Accelerometers are capable of measuring acceleration in one, two or three orthogonal axes. They measure acceleration which is a physical characteristic of a system and convert it in a electric value, such as voltage for example. Acceleration is a measure of how fast the speed is changing as we can see in the equation 3.11.

The international system of units measure acceleration in m/s^2 [41] and considers "g" as a unit of acceleration equals to Earth's gravity at sea level with a value of $9.81m/s^2$ [41].

From all the types of accelerometers two of them stand out. One of them is piezoelectric accelerometer, such as name suggests it works based on the piezoelectric effect. This device has

a piezoelectric quartz crystal on which an acceleration force is applied. The piezoelectric effect is characterized for when the crystal is compressed, the charges accumulate in opposite sides of the crystal contradicting their polarity. In a piezoelectric accelerometer, charge accumulates in the crystal and it is converted and amplified into an output current or voltage. These devices only respond to AC phenomenons such as shock or vibration, rather than DC phenomenons such as acceleration of gravity.

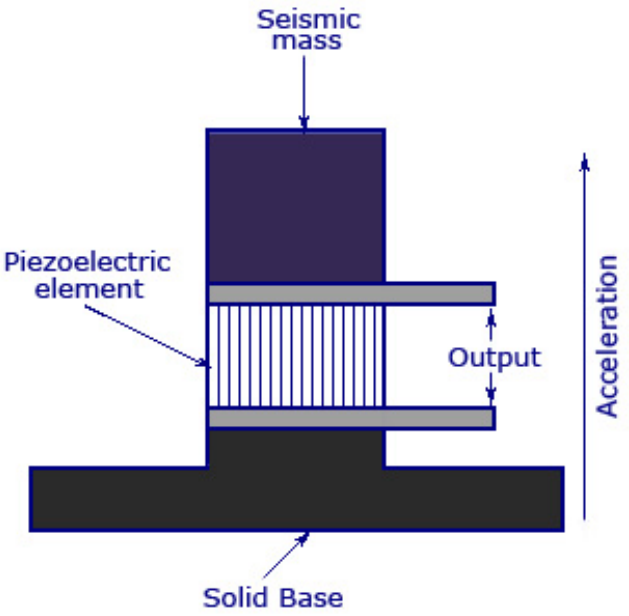

Figure 3.3: Piezoelectric accelerometer [6]

The basis of operating a piezoelectric accelerometer is shown in figure 3.3. This type of accelerometers is usually used in industrial applications and it converts the mechanical action into its corresponding electrical output signal. It works very well at high temperatures and also at frequency rate acquisition up to 100 KHz. Moreover the big advantages of piezoelectric are its wide frequency response, they are intrinsically stable over wide temperature ranges, robust, they can be adapted for different applications and piezoelectric accelerometers output voltages are linear and proportional to measured rates of acceleration which simplifies the signal conditioning. They have among others some common applications such as inertial navigation, drones and unmanned aerial vehicles, vehicle stability control and automation.

The second type of accelerometers that will be described in this study is the capacitive accelerometer. The main advantage of capacitive accelerometers is that no minimal additional processing is

needed, since capacitors can operate both as actuators and sensors. They have a high sensitivity and they work well independently of temperature changes. Capacitive sensing is independent of the base material and depends on the change of capacitance when the geometry of the capacitor is altered. Ignoring the fringing field effect near the edges, the parallel-plate capacitance is [43]:

$$C_0 = \epsilon_0 \epsilon \frac{A}{d} = \epsilon_A \frac{1}{d} \tag{3.6}$$

In equation 3.6 $\epsilon_A = \epsilon_0 \epsilon A$ where A is the area of the electrodes, d is the distance between them and ϵ is the permittivity of the material between the electrodes. Either of these parameters has influence in the capacitance measured and any variation of them will change the capacitance. These variations have been used in MEMS sensing. Thus, accelerometers are based on a change in the distance between the electrodes (d) or in the area of them (A).

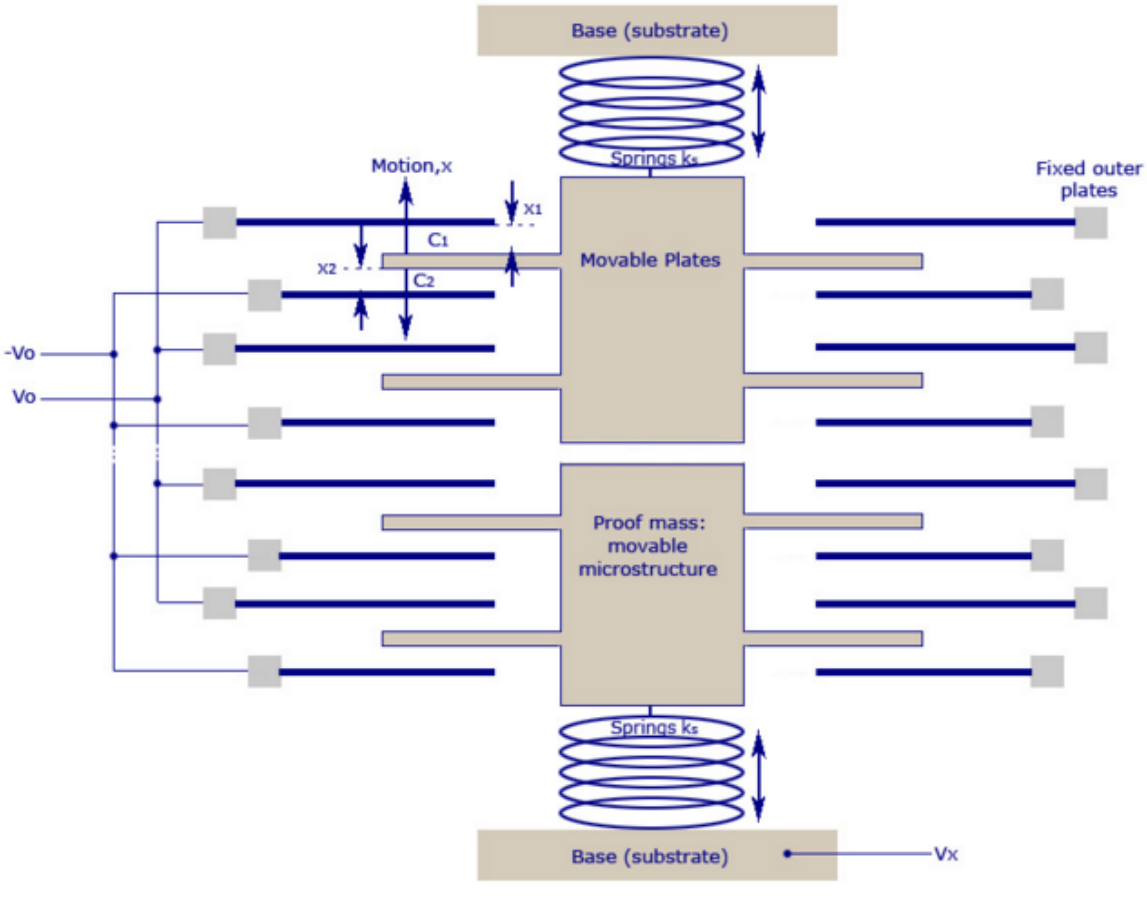

Figure 3.4: Accelerometer structure. The proof mass is attached through springs ($K_s : Springconstant$) at the substrate. In can move only over the vertical axis, up and down. Movable and fixed outer plates construct the capacitors. [6]

As shown in figure 3.4, a typical MEMS accelerometer is composed by a movable $0.1\mu grams$ proof mass with plates that is attached through a mechanical suspension system to a reference frame. Polysilicon springs suspend the structure over the wafer and set a resistance against acceleration forces according with *Hook's Law*. Capacitors are represented by the movable plates and the fixed outer plates with $1.4\mu m$ gaps between the plates[44]. Capacitance difference is the measurement from the deviation of the proof mass. For example, in figure 3.4 the free-space capacitance between the two fixed outer plates and the movable plate C_1 and C_2 is function of the related displacements x_1 and x_2:

$$C_1 = \epsilon_A \frac{1}{x_1} = \epsilon_A \frac{1}{d+x} = C_0 - \triangle C, C_2 = \epsilon_A \frac{1}{x_2} = \epsilon_A \frac{1}{d-x} = C_0 + \triangle C \tag{3.7}$$

Assuming acceleration equals to zero, both the capacitance C_1 and C_2 assume the same value, because $x_1 = x_2 = x$. If $x \neq 0$ the difference between the capacitance C_1 and C_2 is:

$$C_2 - C_1 = 2\triangle C = 2\epsilon_A \frac{x}{d^2 - x^2} \tag{3.8}$$

If $\triangle C$ is measured, x can be found by solving the equation:

$$\triangle C x^2 + \epsilon_A x - \triangle C d^2 = 0 \tag{3.9}$$

Equation 3.9 can be simplified and for small displacements, $\triangle C x^2$ is negligible, thus it might be suppressed. Equation 3.9 can be written as:

$$x \simeq \frac{d^2}{\epsilon_A} \triangle C = d \frac{\triangle C}{C_0} \tag{3.10}$$

From equation 3.10 one concludes that the displacement x is roughly proportional to the capacitance difference $\triangle C$. [43].

As shown in figure 3.4, every sensor has a lot of capacitors sets. All upper capacitors are wired parallel for overall capacitance C_1 and, in the same way, all lower ones for overall capacitance C_2. Otherwise capacitance difference would be too small to detect. This means that equation 3.10 is true for all system and not only for one pair of capacitors. Assuming an ideal spring, according to *Hook's Law*, the spring has a restoring force F_s and this force is proportional to the displacement x, (see figure 3.4). In this way, $F_s = k_s x$, being k_s the spring constant. From *Newton's second law of motion* $F = m \times a = m \times \frac{d^2x}{dt^2}$. Assuming $F = F_s$ the acceleration can be written as a function of displacement:

$$a = \frac{K_s}{m}x \tag{3.11}$$

Making use of measured $\triangle C$ the acceleration will be:

$$a = -\frac{k_s d^2}{m\epsilon_A}\triangle C \tag{3.12}$$

And based on the *Second Newton's Law*

$$ma = m\frac{d^2x}{dt^2} = f_s(x) \tag{3.13}$$

Where f_s is the spring restoring force[43].

3.3 Sensor

As mentioned earlier, an accelerometer is a device that measures two types of acceleration, dynamic acceleration which is experienced by an object relative to free-fall and static acceleration, the change of gravity on a given sensitive axis to determine inclination angles [43]. In the current study, one uses the Analog Devices Accelerometer ADXL335 which is a small, thin, low power, complete 3-axis accelerometer. Table 3.1 sums up the main characteristics of this device.

Table 3.1: Accelerometer ADXL335 characteristics [8]

Characteristic	Range
Sensitive axis	3
Measurement Range	$\pm$ 3.6 g typical
Sensitivity (Radiometric) at each axis	300 mV/g
Operating Temperature	-40 to 85°C
Operating Voltage	1.8 to 3.6V

The sensor is a poly-silicon surface-micro machined structure built on the top of a silicon wafer which details of the structure are described in section 3.1.1. The device also contains signal conditioned analog voltage outputs. This sensor is fabricated based on technology described in section 3.1.2.

The springs represented in figure 3.4 are poly-silicon springs on the respective sensor. These poly-silicon springs suspend the structure over the surface of the wafer and provide a resistance against acceleration forces. The operating mode was described in section 3.2. Remembering figure 3.4, the

sensor's fixed plates are driven by $180\circ$ out-of-phase square waves. This system can be designed as a simple voltage divider whose output is looking forward through a buffer and demodulator.

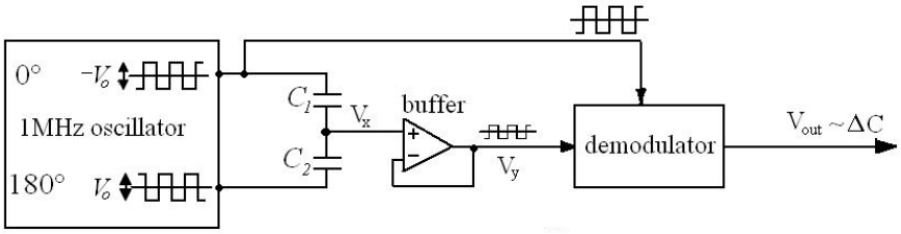

Figure 3.5: Electric circuit that measures acceleration from capacitor changes[7]

Figure 3.5 represents the electric circuit that measures acceleration based on changes from capacitors. Voltage V_x is the voltage of proof mass. Then,

$$(V_x + V_0)C_1 + (V_x - V_0)C_2 = 0 \tag{3.14}$$

and using equations 3.7 and 3.10:

$$V_x = V_0 \frac{C_2 - C_1}{C_2 + C_1} = \frac{x}{d} V_0 \tag{3.15}$$

In equation 3.15 V_x is a square wave with the amplitude proportional to acceleration. When there is not acceleration (a=0) the proof mass does not move, and the voltage output is zero. If acceleration is not equal to zero and positive (a>0), the voltage output V_x changes proportional to alternating input voltage V_0 as one can see in equation 3.15. If we reverse the acceleration (a<0), V_x gets negative sign. Demodulator gives us the correct sign of acceleration, once it multiplies the input signal with the square waves V_0 which come from the oscillator. V_{out} is the output voltage with the right sign of acceleration and amplitude. Now we can write equation 3.11 as proportional to output voltage:

$$a = \frac{K_s d}{m V_0} V_x \tag{3.16}$$

As referred before, the ADXL335 is capable of sensing both static and dynamic acceleration. These two types of acceleration are closely linked with each other and they are present at the output of the sensor as a DC (Direct current) voltage imposed on a AC (Alternating current) signal. The DC voltage has information about the static acceleration which include the angle at which the sensitive

axis is relative to gravity vector. The AC outputs an amplitude voltage which is proportional to the acceleration felt by the sensor relative to its axis of sensitivity.

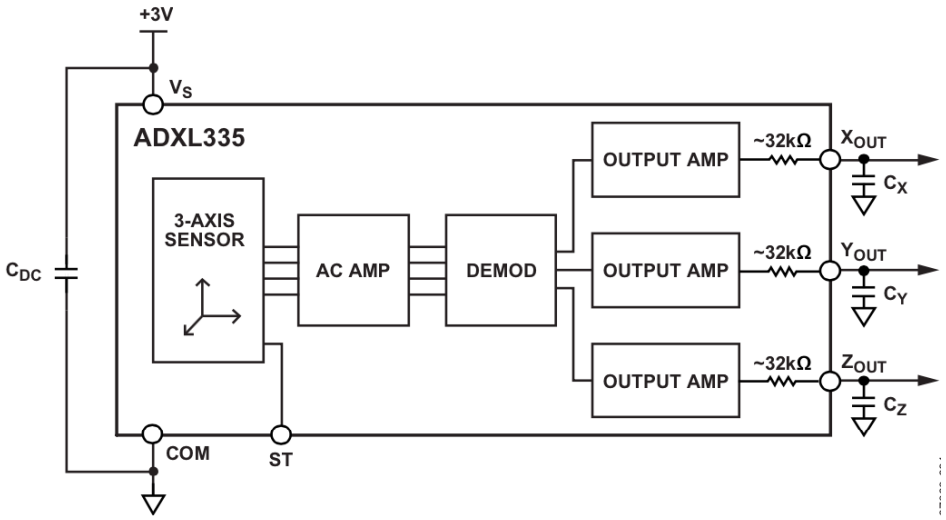

Figure 3.6: Functional Block Diagram of ADXL335[8]

The block diagram of ADXL335 is displayed in figure 3.6 which represents a three-axis accelerometer where there are three setups orthogonally placed similar to figure 3.4.

With the purpose to connect an accelerometer through the bipolar inputs of the EEG equipment, a simple setup was designed.

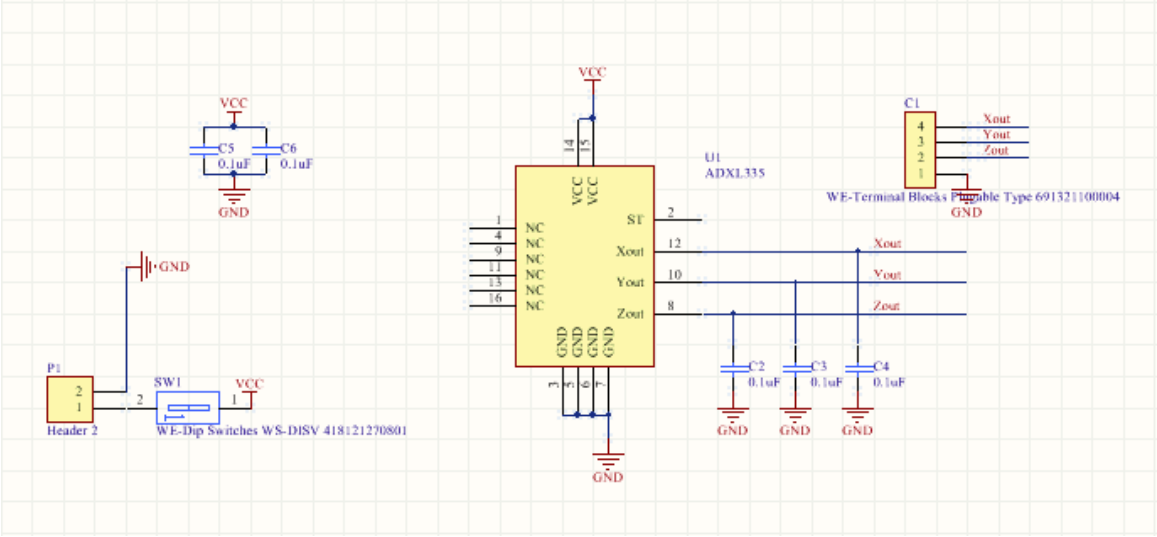

Figure 3.7: Schematic diagram of the ACM device

Figure 3.7 represents the schematic of the ACM (accelerometer) device. The central yellow square represents ADXL335 sensor with nine pins connected. Both VCC pins are connected to a 3.0V battery. All four GND pins are connected to the ground. X_{out}, Y_{out} and Z_{out} represent the output

pins from the three-axis of the accelerometer. Each of these pins have an additional capacitor to set the signal bandwidth of the device. This capacitors were added to implement low-pass filtering for aliasing and noise reduction which is better explained in section 2.4.1. A capacitor of $0.1\mu F$ for C_2, C_3 and C_4 was chosen to set a bandwidth of 50Hz according with the information in ADXL335 data sheet [8]. Sensor outputs are connected to an header with four inputs, three axis and one ground. The connection to the EEG equipment will be made through this header. In the left side of the figure there is another header with a switch. Upper there is a power supply module with two $0.1\mu F$ capacitors, placed closed the ADXL335 supply pins decoupling the accelerometer from noise from the power supply. The accelerometer 3D view is shown in figure 3.8.

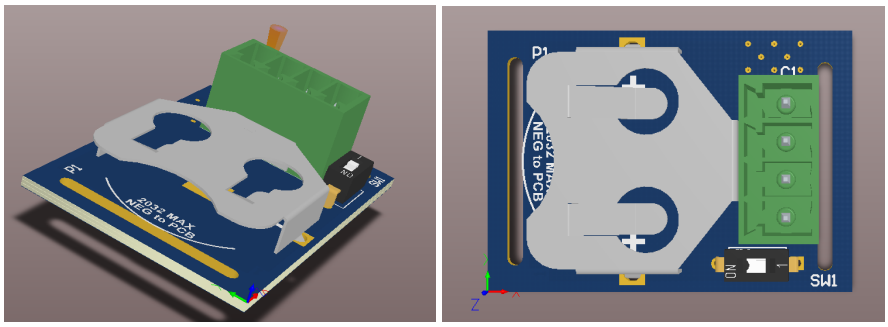

Figure 3.8: Actigraph's evolution

Figure 3.9 shows the device's evolution. In the top left-hand corner is displayed the first circuit designed and manually assembled, in the top-right corner the second version designed in a printed circuit board and in the bottom the last version of the device more small and thin than the others.

To acquire the ACM data, the hardware system with a three-dimensional accelerometer was developed and added to the acquisition unit that already exists. With the set-up represented in figure 3.10, it is possible assess all the signals automatically, temporally synchronized using only one computer's window.

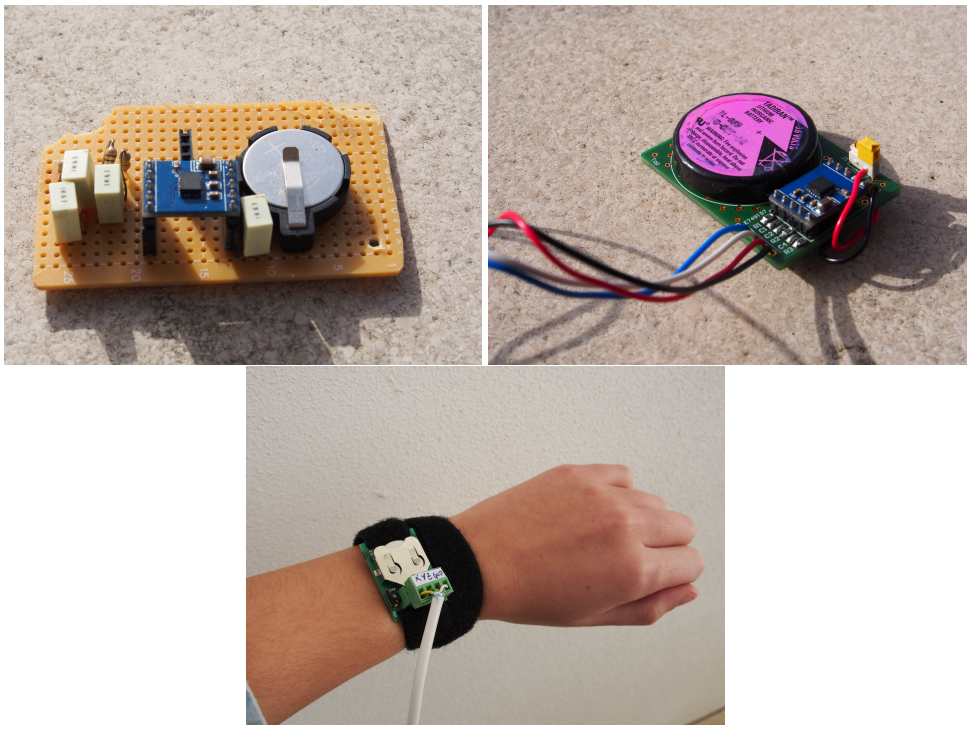

Figure 3.9: Device evolution

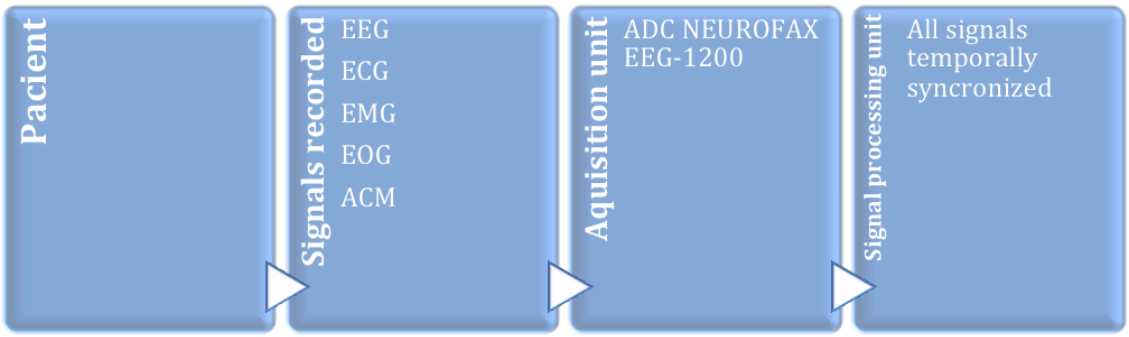

Figure 3.10: Set-up of the patient while monitoring EEG, EMG, ACM, EOG, ECG signals - Block diagram

4

Methods and experimental results

Contents

In this chapter the experimental results will be presented and discussed. Firstly, it was applied an algorithm in Matlab to remove high-frequency noise from the accelerometer signal. Secondly, the data from the accelerometer designed in this study were validated through the correlation with the data from a commercial accelerometer. After that, it was developed an algorithm to detect movement. Finally, it will be presented an analysis of the ACM data to detect the seizure onset.

4.1 Noise filter

For noise analysis the data were acquired through a different acquisition equipment due to resource management reasons. The sampling frequency was 100Hz to this experiment. This data-set was acquired in the "CENC-Centro de Sono" which is a private clinic for studying sleep diseases.

Ideally, for a fixed DC analog input, the output signal should be zero. However, due to noise, this does not happen. This noise is due to thermal noise within the ADC and quantization noise due to the analogue-to-digital conversion process. This noise is usually from Gaussian nature.

This experiment was performed wearing the device myself on my non-dominant wrist while I was moving my arms in aleatory directions.

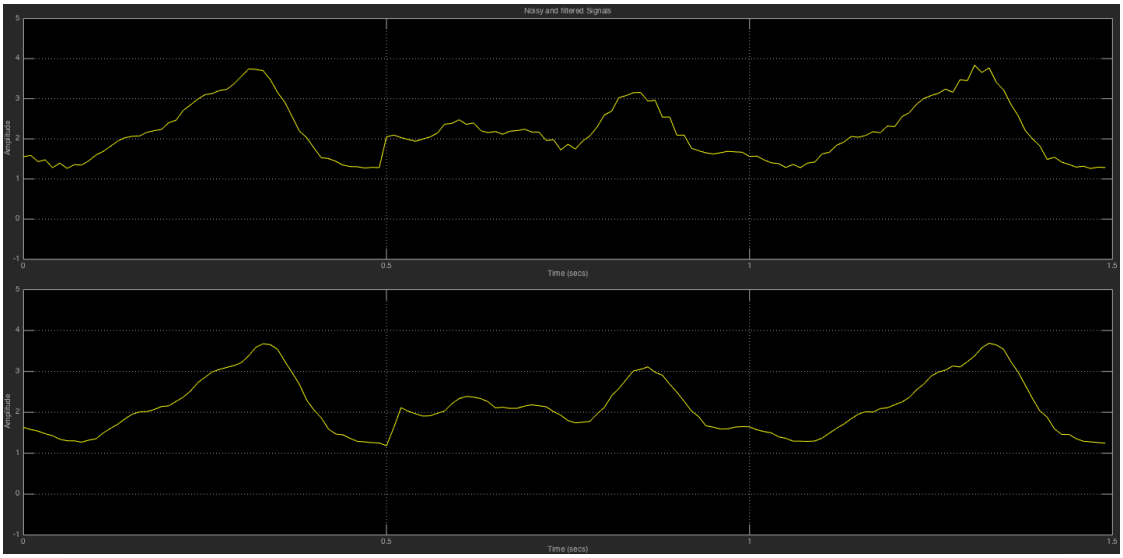

Figure 4.1: Noisy and filtered signal

For noise filtering it was applied a low-pass filter since noise is associated with high frequencies. In order to filtering the "gravitational acceleration" it was added a sequential high pass filter. On the top picture in figure 4.1 it is represented the original signal for 1.5 seconds. On the bottom picture in figure 4.1 it is represented the filtered signal.

For filtering this signal a non-recursive FIR (finite impulse response) filter of order 2 was designed. This was performed with a function from MATLAB *firgr()*. To use this function we must select some parameters. Firstly, we must set the bandwidth intended. Select the Fstop (stop frequency) and Fpass (pass frequency) for the filter. In this case, a band pass filter was computed. After that we have to select the order of the filter and the amplitude vector. Since frequency ripple arises in this filter and in this case the variation means the insertion of loss against increasing frequency, the ripple vector which contains the peak ripple per frequency band must be selected.

Table 4.1: Signal statistics

	Value (V)	Time (secs)
Max	3.756	0.310
Min	1.260	0.490
Peak to peak	2.496	
Mean	2.171	
Median	1.968	
rmsNoise	2.315	

In table 4.1 are presented the signal statistics after filtering noise. The rmsNoise is equal to 2.315 and according to the data-sheet of the sensor [8] the tabulated value for noise density the rms noise is calculated by:

$$rmsNoise = NoiseDensity * (\sqrt{BW \times 1.6}) \tag{4.1}$$

From equation 4.1 the rmsNoise calculated from tabulated value is 2.68. Thus, the relative error in percentage 13.62%.

4.2 Data validation

It is of crucial importance to be sure that the accelerometer designed detects movements as well as a commercial one. With this purpose, the data has undergone a processing mode.

4.2.1 Proposed method

In order to validate the data recorded from the accelerometer designed in the current study, a test using this device and another commercial accelerometer was done and both were placed on the same wrist. MATLAB was used for all processing procedure.

Both data from the accelerometer designed and data from the commercial accelerometer were normalized according to equation 4.2, where $\tilde{X}$ is the normalized value, X is the real value and X_{min} and X_{max} represent the minimum and maximum value, respectively.

$$\tilde{X} = \frac{X - X_{min}}{X_{max} - X_{min}} \tag{4.2}$$

Throughout this experiment the sampling frequency was $F_s = 100Hz$. Figure 4.2 represents a time interval. The horizontal axis represents the samples which correspond to $time(s) \times 100$ and vertical axis represents the signal normalized amplitude.

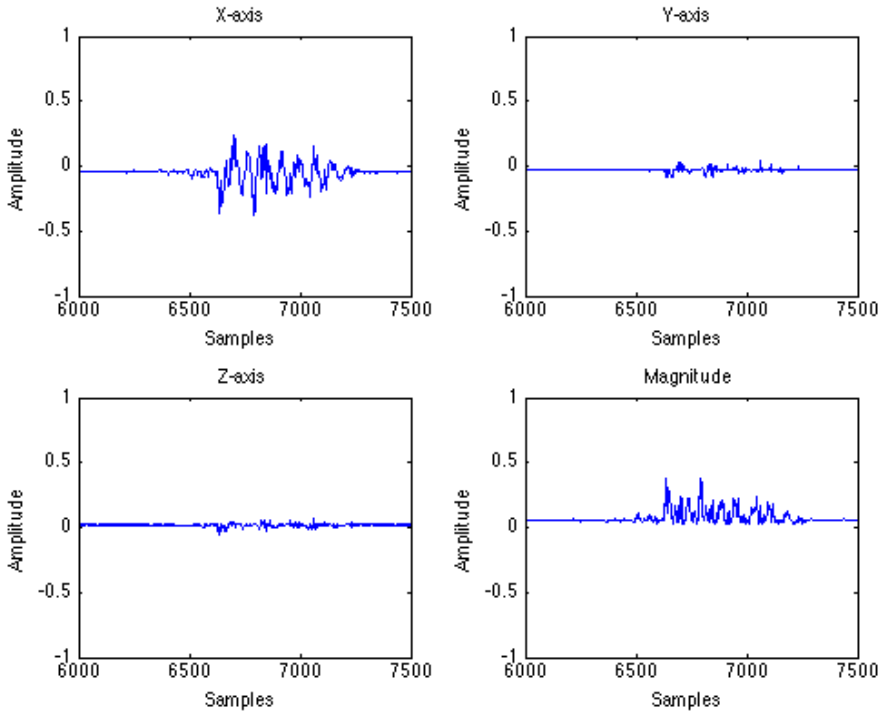

Figure 4.2: Representation of X-axis, Y-axis, Z-axis and magnitude signal.

Since the three axis are orthogonal, the amplitude is calculated through equation 4.3

$$Magnitude = \sqrt{x^2 + y^2 + z^2} \tag{4.3}$$

In figure 4.3 both signals from the accelerometer used in this study and other commercial accelerometer are plotted.

Due to the use of different computers to export the data from the two accelerometers, the data are lagged. In order to align both signals, a simple method was performed. Figure 4.4 displays the

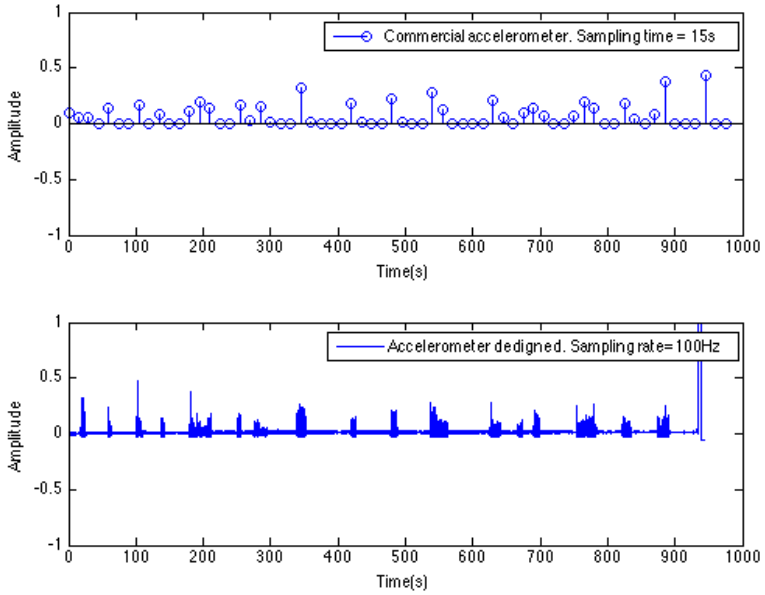

Figure 4.3: Plot of the commercial accelerometer and accelerometer designed signals.

diagram block of the method used to align the two signals. Firstly, it was determined which signal is longer. Secondly, it was computed the cross correlation of the two signals. In signal processing and assuming that these signals are stationary and stochastic processes, the cross correlation r_{yx}can be put in the form:

$$r_{yx} = y(l) * x(-l) \tag{4.4}$$

or for discrete cases,

$$r_{yx} = \sum_{n=-\infty}^{\infty} x(n)y(n-l) \tag{4.5}$$

In both equation 4.4 and equation 4.5 l is the lag parameter.

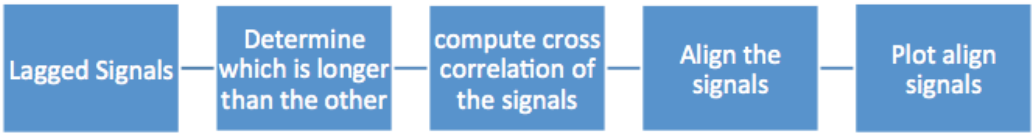

Figure 4.4: Method to align the signals - diagram block

The signal processing toolbox in MATLAB provides a function called **xcorr()** for sequence corre-

lation computation. This function was used in this step to return the lag between the two signals and the cross correlation sequence[45].

After that, the signals were align and then plotted as figure 4.5 shows.

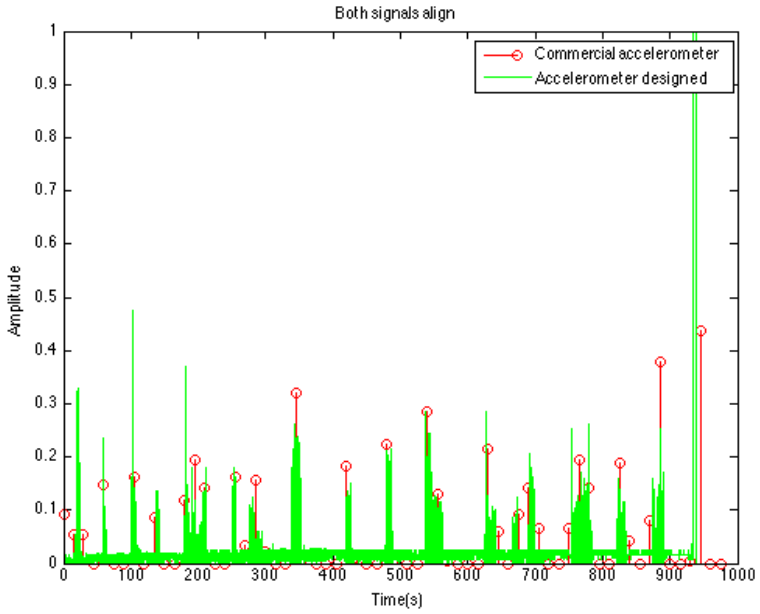

Figure 4.5: Both signals align

4.3 Movement detector algorithm

For movement detection (MD) a simple algorithm was performed. These data were acquired from patients in Hospital Santa Maria and with a sampling frequency of 1000Hz. To that end, a function provided by a toolbox of MATLAB called **findpeaks** was used. Some input values had to be entered, which include the minimum peak height and the minimum distance between peaks. This function finds local maximums throughout the signal and returns the location through index values and the amplitude value. After that, it was created a matrix with binary values.

Thus, the MD is composed by i) a non-causal low pass stretching filter and a ii) threshold (t) binarization block. The width of i) is controlled by the parameter p which selects the time interval to apply the algorithm.

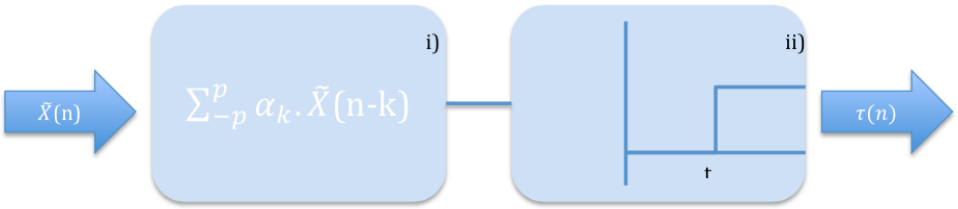

Figure 4.6: Structure of Movement detector (MD)

In figure 4.6 is displayed the structure of the MD algorithm.

For sensitivity which measures the proportion of positive cases that are correctly identified, let:

$$Sensitivity = \frac{TP}{TP + FN} \times 100\% \tag{4.6}$$

For Specificity which measures the proportion of negatives that are correctly identified, let:

$$Specificity = \frac{TN}{TN + FP} \times 100\% \tag{4.7}$$

For precision or positive predictive value which measures the proportion of true positives against the total number of cases, let:

$$PPV = \frac{TP}{TP + FP} \times 100\% \tag{4.8}$$

For accuracy which is the proportion of true results among the total of the cases, let:

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN} \tag{4.9}$$

In the equations above TP means "true positive", TN means "true negative", FP means "false positive" and FN means "false negative". Note that these parameters are a function of the threshold. In this case, it was used a threshold equals to 0.06. The output of the detector is a binary function $\tau(n) \epsilon m, q$, where m corresponds to movement with value '0.1' at the indexes returned by the function **findpeaks** and q corresponds to quietness with value '0'.

In a first approach this algorithm was applied in the signal recorded from the accelerometer designed. In figure 4.7 is displayed the result.

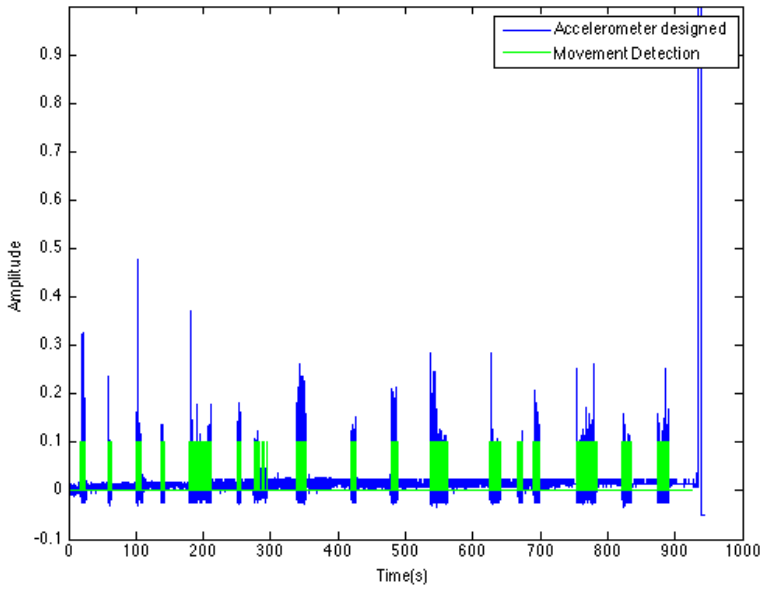

Figure 4.7: Plot of the MD and the original signal from the accelerometer designed

In table 4.2 are displayed all statistical values which were measured from the MD performance throughout the signal recorded.

Table 4.2: Statistical measurements of MD

Sensitivity	$98,26\%$
Specificity	$99,70\%$
Accuracy	$99,68\%$
Precision	$81,79\%$

4.4 Data recorded

The aim of this work is to connect directly an accelerometer through a bipolar input of the EEG equipment in order to make available in the same window all signals. Therefore, the accelerometer described in the previous chapter was used. As in previous subsection, these data were acquired in Hospital Santa Maria with a sampling frequency of 1000Hz.

Figure 4.8 is a print screen of the system software where are shown all signals recorded in the same window. The data recorded from the accelerometer are represented in the last three channels. These data were recorded from a child while he was in a long-term EEG monitoring in Hospital Santa Maria over five days. In the figure, a paroxysmal event is represented as well as the changes over all channels. If one assess all the signals can conclude that when the paroxysmal event begins

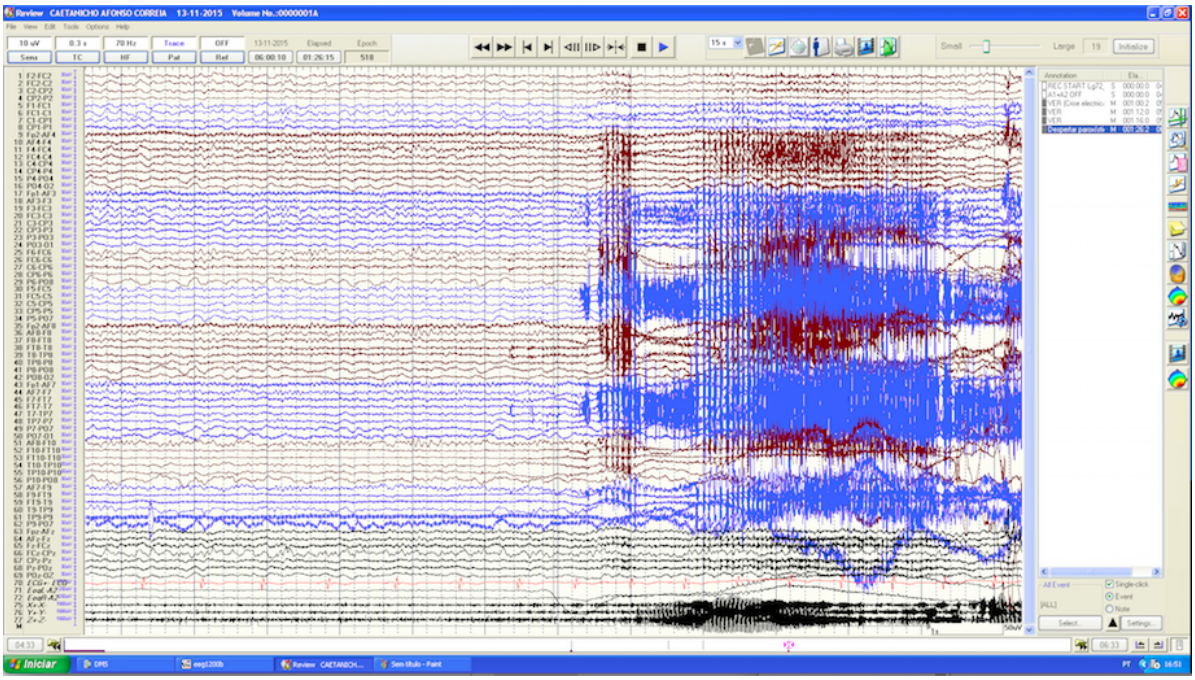

Figure 4.8: All signals recorded represented in the same window

the amplitude and frequency of all signals increased drastically. Assessing all signals it is easy to extrapolate when the event begun. As we can see in figure 4.8, alterations in ACM data occurred less than one second later. The window's width is fifteen seconds. A paroxysmal event may be epileptic seizures whether the abnormal behaviours are caused by excessive, hyper synchronous activity of the neurons in the brain[46].

In figure 4.9 are represented other paroxysmal events from the same patient. An awakening event was identified and may be followed by an electric seizure. In this case the data are almost synchronized with the changes over the other channels.

4.4.1 Data analysis

In order to prove that actigraphy is a good tool to identify an epileptic seizure, the data recorded from different patients through EEG equipment in Hospital Santa Maria were processed and analysed.

Figure 4.10 display a block diagram about the method that was used to process and analyse the data.

1. Firstly, data must be converted to be processed in MATLAB. This step is divided in two steps: Convert data to European data format (*.edf*) which is a simple and flexible format for exchange and storage of multichannel biological and physical signals and then, convert data to a set

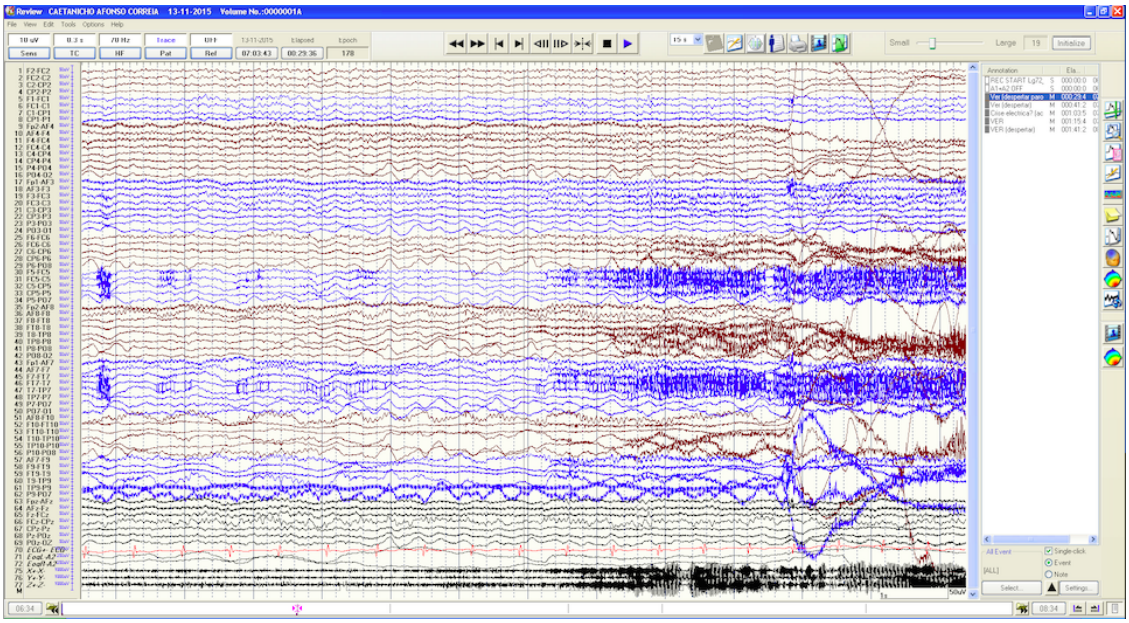

Figure 4.9: All signals recorded represented in the same window. Paroxysmal event and possible electric seizure. It was assessed by doctor as an epileptic seizure

legible by MATLAB. After that, data was converted using a toolbox from matlab called EEGLAB to convert to .set format.

2. Since the data was acquired from bipolar inputs channel operations must be done. These are simple subtract operations where the inactive input is subtracted from the active input.

3. A stretching filter was applied over the time interval during which seizures was detected by doctors. In addition, data was normalized and filtered with a low-pass filter to filter high frequency noise and with a high pass filter to filter "gravitational acceleration". Figures 4.11 and 4.12 show the magnitude and phase response for the bandpass filter, respectively.

4. Event marks were made by technicians and afterwards assessed by a doctor as being or not a seizure. Furthermore, MD algorithm was performed to detect movement at the onset of the seizures.

Two epochs of 20 seconds each were selected to analysis. The first 20 seconds is the time before the event mark and the last 20 seconds is the time after the event mark. The event was marked at 20 seconds. For this experiment, 62 events were marked by doctors and then they were analysed, 46 seizures, 9 paroxysmal events, 6 unknown events and 1 awakening forced.

Figure 4.13 displays one of the seizures in which was applied MD algorithm to detect the seizure

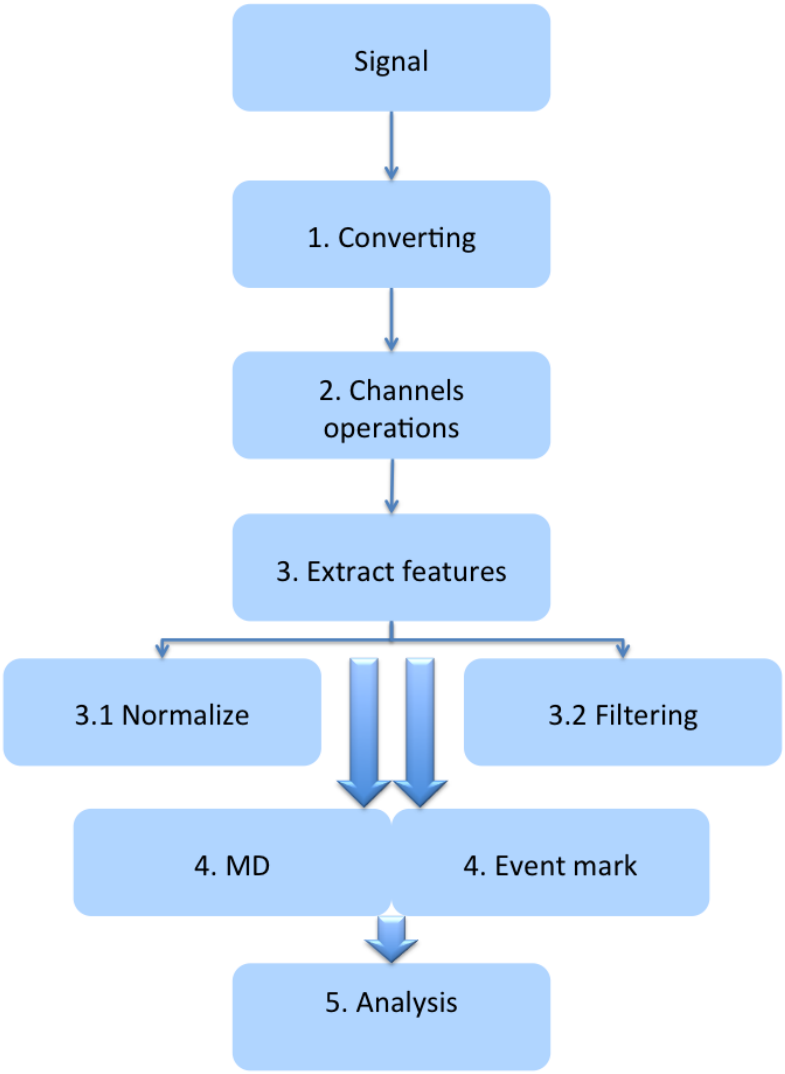

Figure 4.10: Method to analyse the data recorded from patients while they worn an accelerometer

onset. The event was marked by doctor and it is temporally synchronised with involuntary movements start. The validation was done by comparison between the video and the ACM signal. Sometimes, depending on where the seizure onset is in the brain, motor activity may be interrupted during the seizure. In figure 4.14, the seizure onset matches an activity arrest period marked with yellow colour and the recover time is marked with red colour.

On the other hand, there may be no relevant changes in movement patterns at the time that the patient is having an epileptic seizure. Figure 4.15 shows an example of this type of seizures.

The MD algorithm was applied over all signals to assess its performance. For that, sensitivity, specificity and accuracy of the algorithm were calculated. These equations were described in section 4.3.

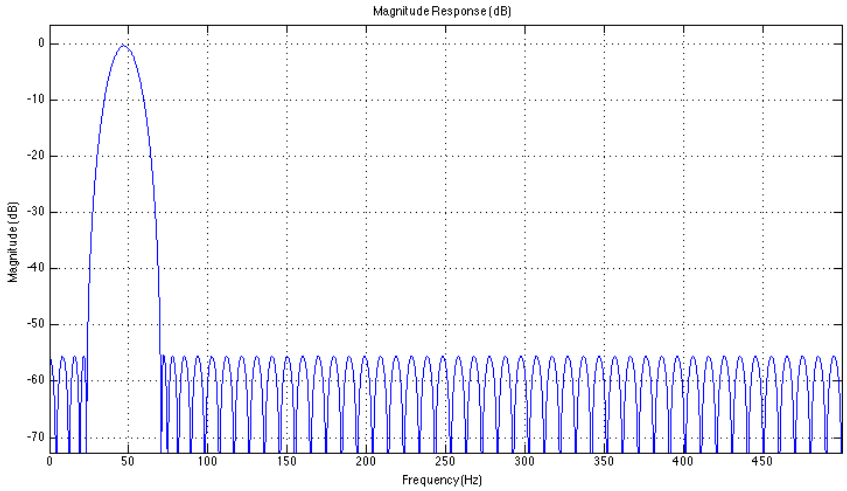

Figure 4.11: Bandpass filter - magnitude response applied through the data that were acquired with a sampling frequency of 1000Hz.

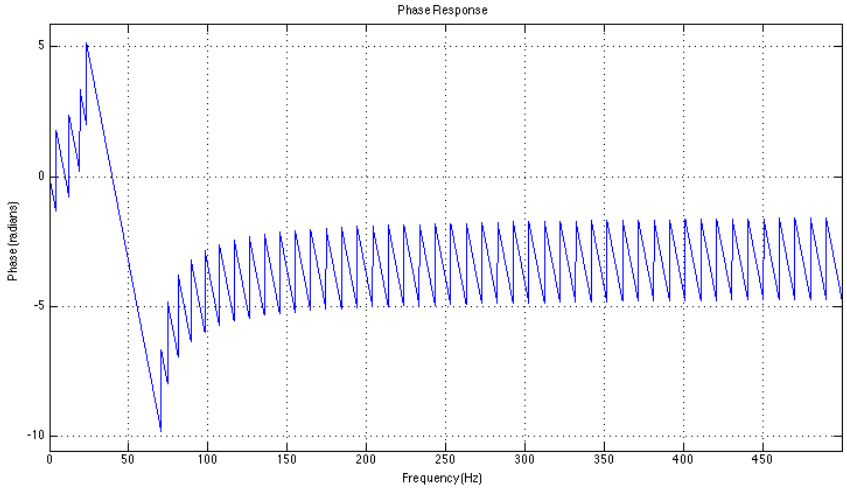

Figure 4.12: Bandpass filter - phase response applied through the data that were acquired with a sampling frequency of 1000Hz.

Let

- True positive - a test in which the result is positive and it really is. In other words, the algorithm detects movement and the patient was really moving his arm.
- False positive - a test in which the result is positive and it is not true. In other words, the algorithm detects movement and the patient was quiet.
- True negative - a test in which the result is negative and it really is. In other words, the algorithm does not detect movement and the patient was really quiet.
- False negative - a test in which the result is negative and it is not true. In other words, the

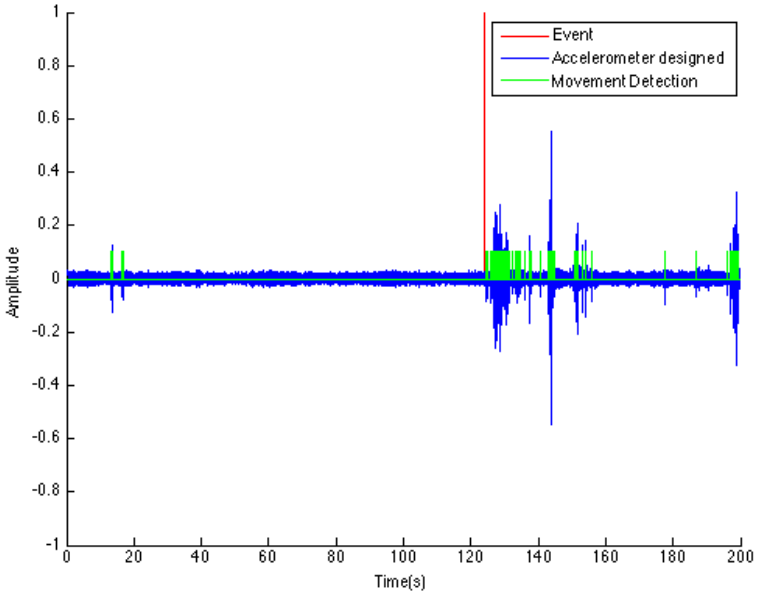

Figure 4.13: Example of MD in one of the seizures

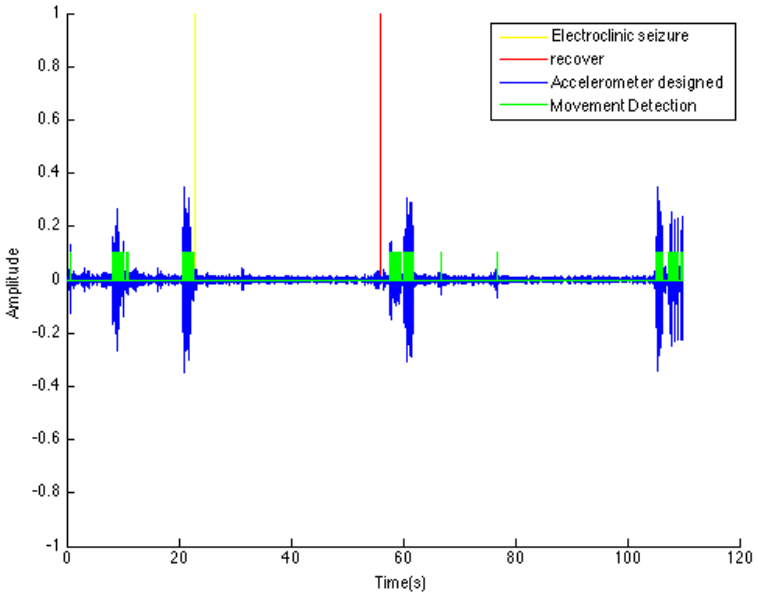

Figure 4.14: Example of MD in one of the seizures

algorithm does not detect movement and the patient was moving his arm.

Table 4.3: MD performance

Sensitivity	$74,00\%$
Specificity	$98,28\%$
Accuracy	$96,80\%$

The parameters displayed in table 4.3 were calculated for each event and then the average of

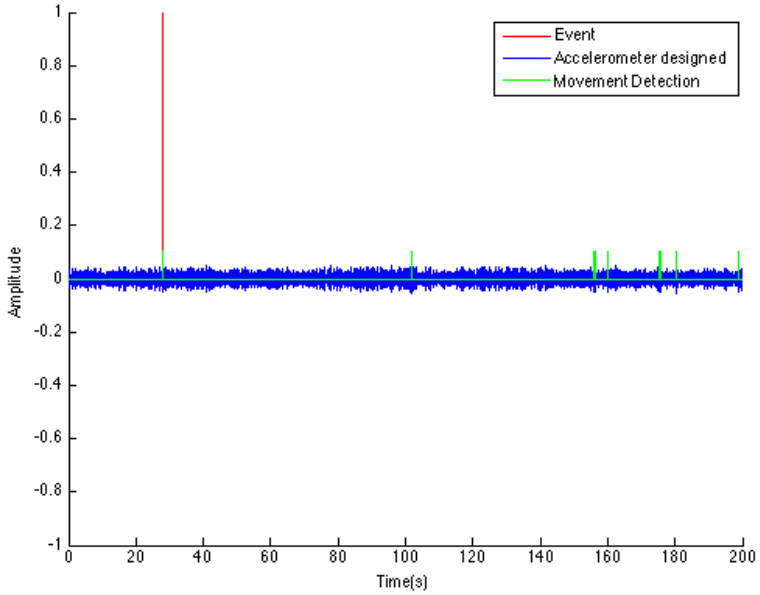

Figure 4.15: Example of MD in one of the seizures

all was estimated. The gross results are shown in appendix A where it is displayed the results for algorithms performance in each seizure.

This method can reduce a lot the length of data to analyse by doctors but it also have a lot of false positives, since it detects all movements, even if they are not related with the seizure onset.

4.4.2 Algorithm to detect seizures onset

With the purpose of detecting seizures onset, an algorithm was developed to identify patterns at the time that seizure starts. To achieve this, it was implemented a theoretical framework called matched filter which is an ideal filter to process a received signal. The matched filter maximises the SNR of the filtered signal and has an impulse response that is a reverse time-shifted version of the input signal.

Let the received signal be $s_0(t) + n_0(t)$ and $s(t)$ the transmitted signal:

$$s[t] \Longrightarrow s_0[t] + n_0[t]$$

$s[t]$ goes through a filter with impulse response $h[t]$, and picks up noise $n[t]$ along the way. The transformation occurs inside the linear time invariant system (LTI) called matched filter. LTI transformation is the single most important relationship in the field of communications since it gives us a way

to relate input and output signals,

$$x[t] \Longrightarrow h[t] \Longrightarrow y[t]$$

The output at any moment in time will be:

$$y[n] = \sum_{k=-\infty}^{\infty} \alpha_k h[n-k]$$

Thus, the response of LTI is the summation of the weighted and shift input pulses. In time domain it is the convolution between the impulse response of LTI and the signal received: $y(t) = h(t) * x(t)$.

It is important to draw attention to two different types of changes in movement at the time that seizure starts. Some seizures are characterized by involuntary movements and others by activity arrest. Thus, the sets were divided according with the way that movement changed.

Table 4.4: Sets selected

	Seizure		No seizure	
	Involuntary movements	Activity arrest	Movement	Quietness
Number of training data-sets	7	5	-	-
Number of test data-sets	15	6	33	16

It was selected a trainee data-set in which the patient starts movements and other trainee set in which the patient starts a quietness period.

Firstly, all data-sets are filtered following the same method described in section 4.1. After that, they are filtered again with a low pass filter and then the sampling frequency was reduced by a factor of 100. This reduction was done with **decimate()** function in MATLAB. Figure 4.16 and figure 4.17 display the magnitude response and phase response of the low-pass filter, respectively.

Secondly, the average signal $\bar{X}(t)$ of the trainee data-set must be calculated:

$$\bar{X}(t) = \frac{1}{N} \sum_{i=1}^{N} x_i(t) \tag{4.10}$$

In equation 4.10 N is the number of trainee data-sets and $x_i(t) is the element of each data-set at time t. The average sig$

The $h(t)$ was fitted and this fitted signal will be the signal input for the matched filter displayed in figure 4.18.

As we have a time-domain template, its matched filter is a time-reversed version of itself. For that a function called **flipud()** was used. This function returns a vector with the same length of the

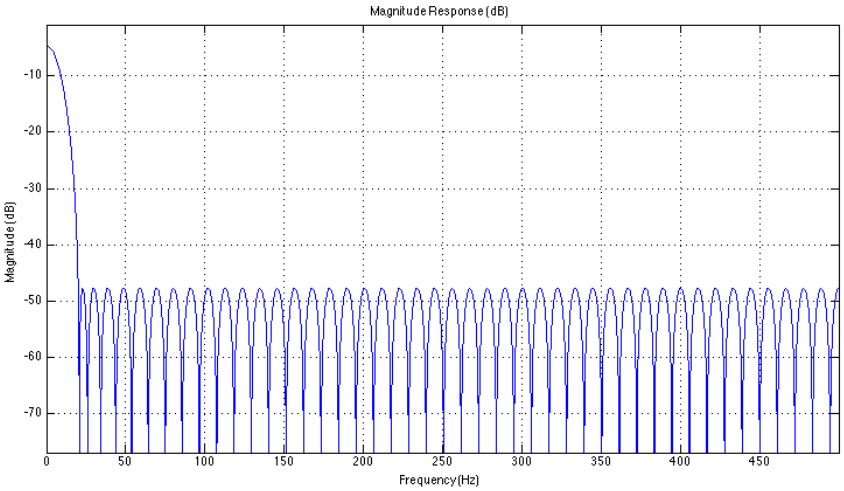

Figure 4.16: Low-pass filter - magnitude response

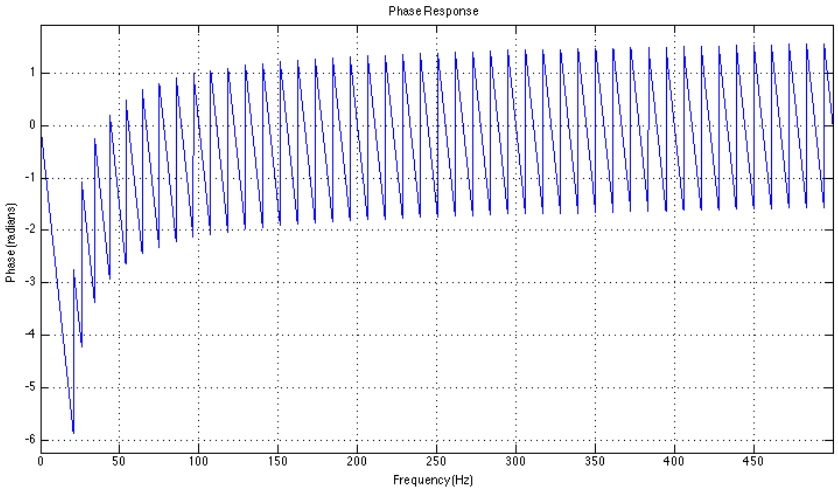

Figure 4.17: Low-pass filter - phase response

input column vector with the order of its elements reversed. The matched filter is nothing else than a correlate that correlates with a given signal pattern.

Figure 4.19 displays the method to apply matched filter in an input signal. The input signal in this figure is the signal to analyse. An average signal that results from the average signal of the trainee set is added in a filter as a reference signal. This filter will find the epochs that are similar to the reference signal and mark them with a spike. In short, the output signal is obtained by correlation of a known signal(average signal) with an unknown signal to detect the presence of the input signal in the analysed signal.

The data analysed by this filter were selected after the movement detection algorithm was applied.

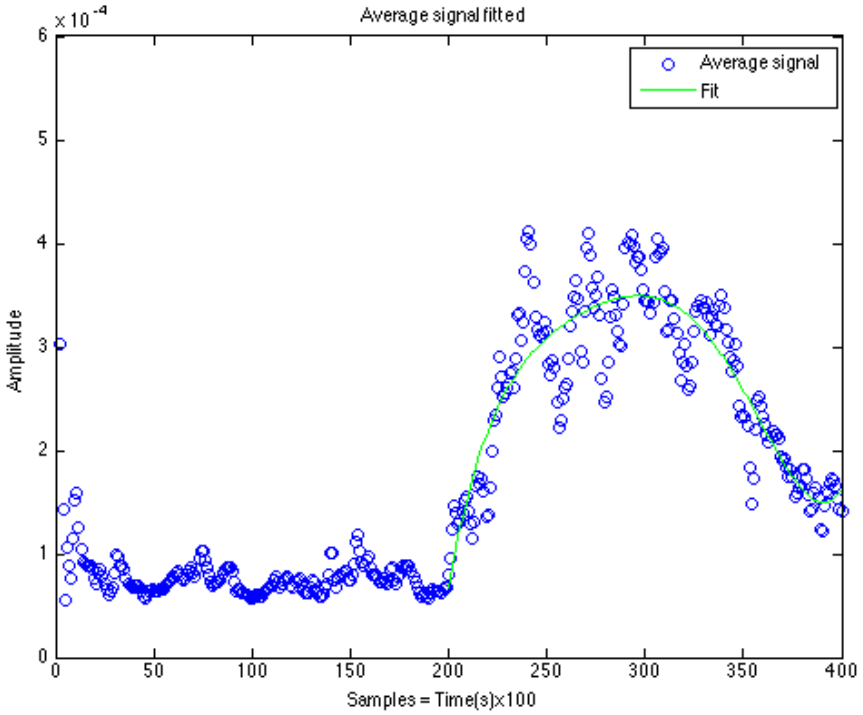

Figure 4.18: Average signal fitted with a polynomial curve for seizures that at t=20s starts movement, equation: $y(t) = a5 \times x(t)^5 + a4 \times x(t)^4 + a3 \times x(t)^3 + a2 \times x(t)^2 + a1 \times x(t) + a0$

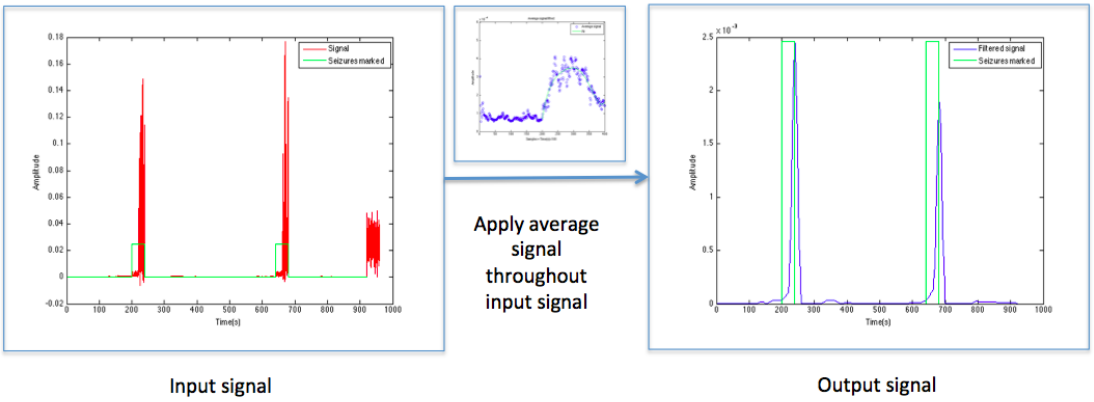

Figure 4.19: Method to apply matched filter throughout an input signal

Only were analysed data with seizures in which there was movement, both involuntary movements as well as activity arrest. The training data-set was different for data in which there was activity arrest and involuntary movements, but both worked well. Firstly, we analysed the data from seizures which manifest themselves by involuntary movements. Figure 4.20 displays the signal from accelerometer (blue line), the marks made by doctors (green intervals) in epochs of 40 seconds, and the spikes found by the algorithm. Fifteen seizures were marked and the algorithm only found eleven. So, for this data-set the algorithm achieves the statistical values :

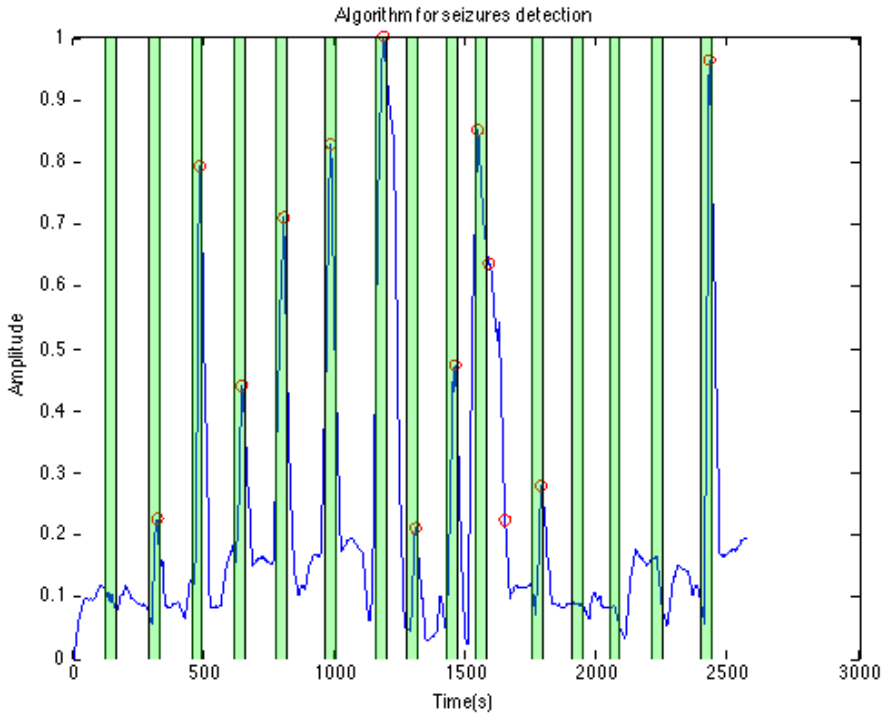

Figure 4.20: Seizures detection algorithm results for data in which seizures manifest themselves by starting movement.

- Sensitivity = 73.33%
- Specificity = 95.74%
- Accuracy = 90.32%
- PPV = 84.63%

PPV is the positive predictive value which is the proportion of positive results that are truly positive. These statistical parameters result from equations in section 4.3.

Secondly, we applied the algorithm throughout a data set with other events marked like paroxysmal events and forced awakenings. Figure 4.21 displays results for seizures (green interval) and events (red interval) detection after running the algorithm throughout these data.

Considering both seizures and other events marked in EEG signal, we achieve better values for statistical parameters:

- Sensitivity = 84.62%
- Specificity = 95.74%

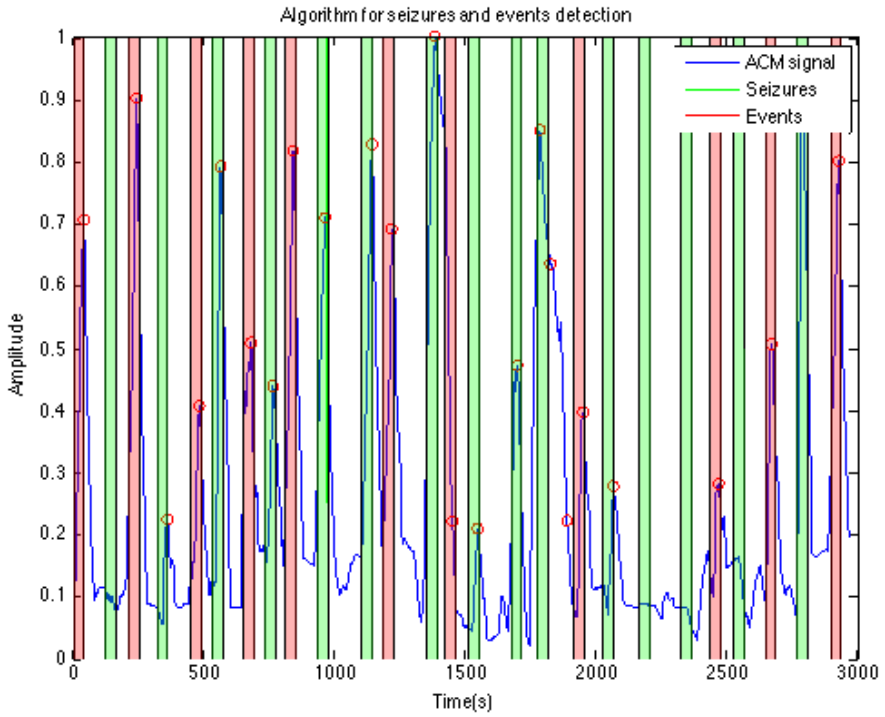

Figure 4.21: Seizures and events detection algorithm results for data in which seizures manifest themselves by involuntary movements.

- Accuracy = 91.78%
- PPV = 91.77%

The data set in which seizures manifest themselves by activity arrest movement were also analysed. Figure 4.22 displays the input signal to be tested by matched filter and figure 4.23 displays the output signal of the matched filter. In this case:

- Sensitivity = 92.30%
- Specificity = 80.00%
- Accuracy = 84.21%
- PPV = 70.59%

In an overall analysis we achieved statistical values with a sensitivity of 83.42%, specificity of 90.49%, accuracy of 88.77% and a positive predictive value of 82.33% which means we succeeded to detect seizures that are truly seizures. As one can see in figure 4.22 there are some epochs without seizures that have movement. The algorithm tests the signal's shape.

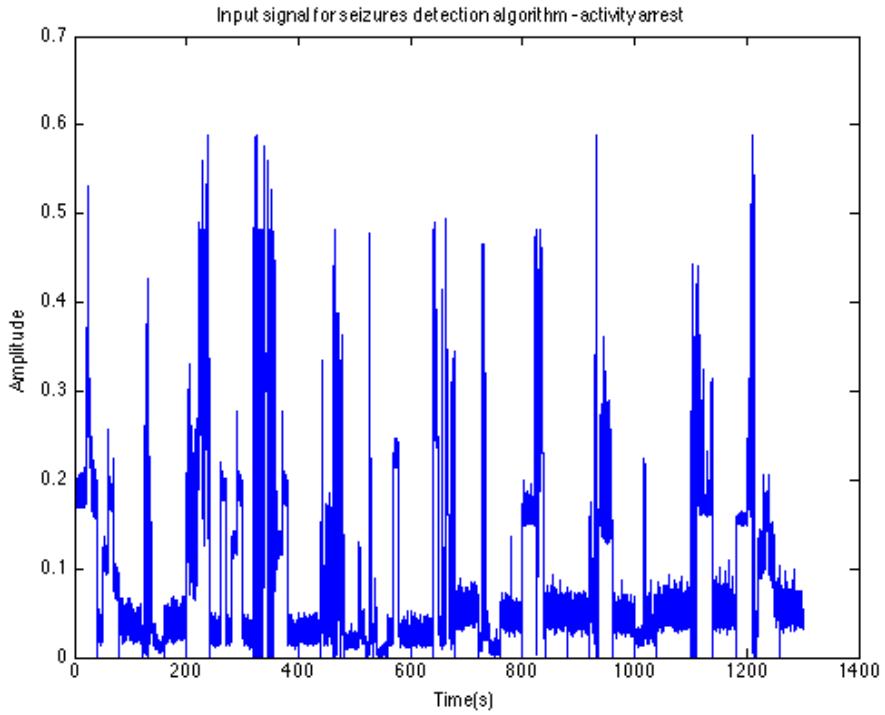

Figure 4.22: Input signal for data in which seizures manifest themselves by activity arrest.

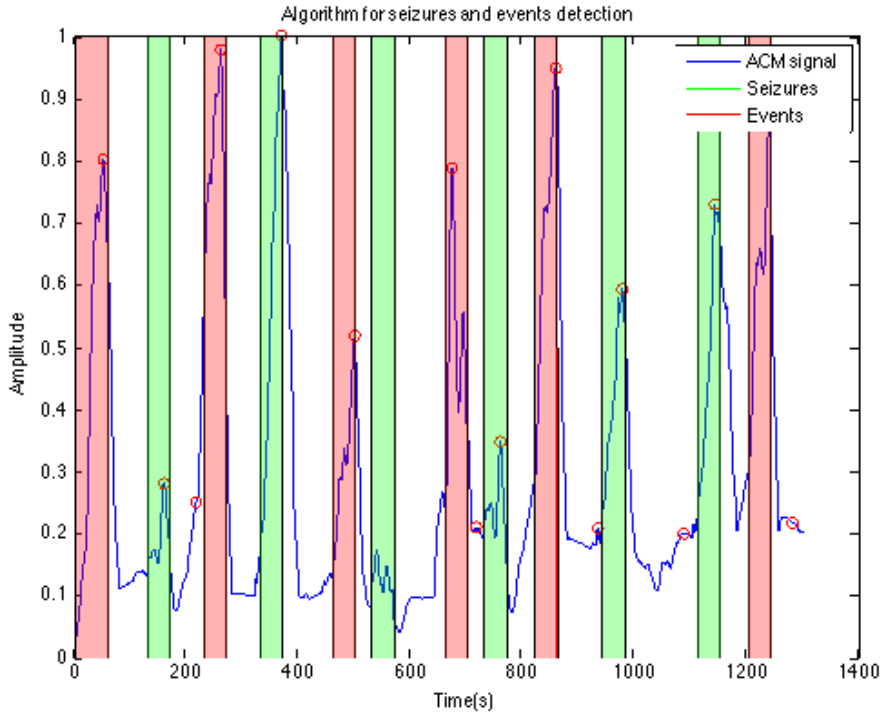

Figure 4.23: Seizures and events detection algorithm results for data in which seizures manifest themselves by activity arrest.

Table 4.5: Gross results for the algorithm with seizures and events detection

Seizures	Seizures detected		Event	Event detected	
Y	N	FN	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	N	FN	Y	Y	TP
Y	N	FN	Y	Y	TP
Y	N	FN	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	Y	TP	Y	Y	TP
Y	N	FN			
Y	Y	TP			
Y	Y	TP			
Y	Y	TP			

Table 4.6: Gross results for the algorithm with no events or seizures detection

No Seizures or events	Event detected		No Seizures or events	Event detected		No Seizures or events	Event detected	
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	Y	FP	Y	N	TN	Y	Y	FP
Y	Y	FP	Y	N	TN	Y	Y	FP
Y	N	TN	Y	N	TN	Y	Y	FP
Y	N	TN	Y	N	TN	Y	Y	FP
Y	N	TN	Y	N	TN	Y	Y	FP
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN	Y	N	TN	Y	N	TN
Y	N	TN						

The gross results of the algorithm performance throughout all data analysed are displayed in tables 4.5 and 4.6. Table 4.5 shows results for seizures and events detection and table 4.6 shows

results for no seizures or events data. If we take into account only seizures detection, the values of sensitivity, specificity, accuracy and positive predictive value are 76.19%, 89.55%, 86.36% and 69.57%, respectively, which means that a good proportion of positives that were identified as such and the aim of this study was achieved.

5

Conclusions and Future Work

The goal of this study was to use a tool called actigraphy, which has already been used to monitor other neurological diseases, for monitoring patients with epilepsy. Since all measurements of the different signals were made by the same equipment, the accelerometer was connected through the bipolar inputs of the same equipment. In this way, the big advantage of this work is that these signals were temporarily synchronized with all others, which makes easier identifying the instant at which the seizure started. This will ease the work of technicians and doctors which is nowadays a very time consuming work.

Firstly, a simple electronic circuit was designed to connect the sensor to the EEG equipment. The first step was to measure the signal to noise ratio and compare this value with the tabulated value. The tabulated value is 2.68 and the value measured is 2.315. The SNR measured is less than the value tabulated because it was tested in a noisy environment due to all equipments that usually work in the infirmary apart from EEG equipment, video and others for transferring data.

Secondly, the validation of data was done. For this aim, cross-correlation of all the data was done with data from a commercial accelerometer and from the accelerometer designed for this study. We conclude that the data from the accelerometer matched well with the data from the commercial accelerometer.

In order to identify movement changes an algorithm for movement detection was developed. First, it was applied on the data used for validation. The algorithm had a sensitivity of 98.26%, a specificity of 99.70%, an accuracy of 99.68% and a precision of 81.79%.

The data acquired from patients with epilepsy was then analysed. The movement detection algorithm was applied over 46 seizures and 16 events and a manual validation was done, achieving a sensitivity of 74%, a specificity of 98.28% and an accuracy of 96.80%. This validation was done by plotting in the same figure movement detection results, ACM signal and events marked by doctors. Due to the fact that this algorithm detects all movements, it has a lot of positives that are not seizure (the statistical values are only for movement detection).

An algorithm for seizure detection based on signal patterns at the time that the seizure onset was marked by the doctor was developed. This algorithm detects seizures automatically through epochs of 40 seconds, in which the seizure is marked at 20 seconds. The data analysed by this algorithm came from the movement detection algorithm. It only were analysed seizures and events which manifest

themselves by involuntary movements or sudden activity arrest. It achieves a sensitivity of 76.19%, a specificity of 89.55%, an accuracy of 86.36% and a positive predictive value of 69.57%. These measurements are for both seizures which manifest themselves by activity arrest or by involuntary movements. We made the same analysis for both seizures and events detection and in this case we achieved higher values of sensitivity, specificity, accuracy and positive predictive value of 83.42%, 88.77%, 90.49% and 82.33%, respectively. The detection of events achieved the maximum values for these parameters because the algorithm succeeded in detecting all events and so the statistical values increased.

From all experiments, we understand that some improvements should be done in the algorithms. The results could be statistically more relevant if there were more data from different patients. It is difficult to acquire measurements because data is acquired in real patients over one week of continuous monitoring of video and EEG.

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AppendixA

Table A.1: Gross results for movement detector algorithm

Event type	Filtered	Event detected			MD		
		Y/N	Feature assessed	Comments	Sensitivity	Specificity	Accuracy
Seizure	Yes	Y	stop movement	start of a quietness period	75,00%	94,01%	94,01%
Seizure	Yes	Y	stop movement and recovered time	start of a quietness period and recover after some seconds	66,67%	99,87%	99,86%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	80,00%	98,46%	98,46%
Seizure	Yes	N			75,00%	100,00%	100,00%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	66,67%	99,55%	99,55%
Seizure	Yes	N	No differences in movement		66,67%	99,55%	99,55%
Seizure	Yes	Y	start movement	one spike at the same time of the seizure onset	75,00%	99,75%	99,75%
Seizure	Yes	Y	stop movement	three consecutive spikes that are followed by a quietness period	66,67%	99,83%	99,83%
Seizure	Yes	N	No differences in movement	long period of quietness	66,67%	99,97%	99,97%
Seizure	Yes	Y	start movement	frequency and amplitude of the signal was increased after a period of low amplitud and frequency	85,71%	94,81%	94,81%
Seizure	Yes	N	No differences in movement	electroclinical seizure	66,67%	99,91%	99,91%
Seizure	Yes	Y	stop movement		80,00%	98,91%	98,91%
Event mark	Yes	Y	start movement		66,67%	99,37%	99,37%

Table A.2: Gross results for movement detector algorithm. Continue

Event type	Filtered	Event detected			MD		
		Y/N	Feature assessed	Comments	Sensitivity	Specificity	Accuracy
Event mark	Yes	Y	changes in movement patterns	frequency of the signal was increased	85,71%	97,22%	97,22%
Event mark	Yes	Y	changes in movement patterns		80,00%	98,38%	98,38%
Event mark	Yes	Y	stop movement		85,00%	97,84%	97,84%
Seizure	Yes	Y	stop movement	start of a quietness period	85,71%	99,51%	99,51%
Seizure	Yes	Y	stop movement	a high spike followed by waves with much lower amplitude	80,00%	93,87%	93,87%
Event mark	Yes	N			50,00%	99,95%	99,95%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	75,00%	99,60%	99,60%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	70,83%	99,18%	99,18%
Paroxysmal	Yes	Y	start movement	start spikes at the same time that was marked a paroxysmal event	96,88%	99,02%	99,02%
Paroxysmal	Yes	Y	start movement	start spikes at the same time that was marked a paroxysmal event	87,50%	99,65%	99,65%
Seizure	Yes	N			50,00%	99,99%	99,99%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	66,67%	99,52%	99,52%
Seizure	Yes	Y	stop movement	start of a quietness period	75,00%	99,65%	99,65%
Seizure	Yes	Y	start movement	one spike lagging 10s behind the seizure mark	75,00%	99,96%	99,96%
Seizure	Yes	Y	start movement	start spikes with high amplitude and frequency at the same time that was marked a seizure	75,00%	96,61%	96,61%
Seizure	Yes	N	No differences in movement		71,73%	94,19%	94,19%

Table A.3: Gross results for movement detector algorithm. Continue

Event type	Filtered	Event detected			MD		
		Y/N	Feature assessed	Comments	Sensitivity	Specificity	Accuracy
Seizure	Yes	Y	Sudden decrease of amplitude and frequency	electroclinical seizure	85,71%	95,90%	95,90%
Seizure	Yes	Y	start movement	electroclinical seizure	80,00%	97,41%	97,41%
Seizure	Yes	Y	stop movement	electroclinical seizure	75,00%	98,91%	98,91%
Seizure	Yes	Y	start movement	start spikes with high amplitude and frequency at the same time that was marked a seizure	76,92%	95,87%	95,87%
Seizure	Yes	Y	stop movement	start of a quietness period	76,92%	97,60%	97,60%
Seizure	Yes	N			66,67%	99,99%	99,99%
Seizure	Yes	Y	Sudden decrease of amplitude and frequency	a high spike followed by waves with much lower amplitude and frequency	66,67%	96,55%	96,55%
Seizure	Yes	Y	stop movement	start of a quietness period	80,00%	95,70%	95,70%
Seizure	Yes	Y	start movement	start spikes with high amplitude and frequency at the same time that was marked a seizure	83,33%	96,09%	96,09%
Seizure	Yes	N			50,00%	99,97%	99,97%
Seizure	Yes	Y	start movement	start spikes with high amplitude and frequency at the same time that was marked a seizure	79,17%	97,85%	97,85%
Seizure	Yes	N			80,00%	99,99%	99,99%
Seizure	Yes	N		paroxysmal event follow the seizure	89,89%	99,46%	99,45%
Paroxysmal	Yes	Y	start movement				
Seizure	Yes	N			50,00%	99,98%	99,98%
Seizure	Yes	Y	start movement	a spike followed by a quietness period	66,67%	99,26%	99,25%

Table A.4: Gross results for movement detector algorithm. Continue

Event type	Filtered	Event detected			MD		
		Y/N	Feature assessed	Comments	Sensitivity	Specificity	Accuracy
Paroxysmal	Yes	Y	start movement	a spike followed by a quietness period	73,68%	99,64%	99,64%
Seizure	Yes	N	No changes		50,00%	99,54%	99,54%
Paroxysmal	Yes	Y	start movement	start spikes at the same time that was marked a paroxysmal event	84,21%	98,64%	98,64%
Paroxysmal	Yes	Y	start movement	start spikes at the same time that was marked a paroxysmal event	66,67%	99,58%	99,58%
Paroxysmal	Yes	Y	start movement	start spikes at the same time that was marked a paroxysmal event	85,71%	98,65%	98,65%
Seizure	Yes	N	No differences in movement		66,67%	99,95%	99,95%
Paroxysmal	Yes	N	No differences in movement		66,67%	99,81%	99,81%
Seizure	Yes	Y	start movement	start spikes at the same time that was marked a seizure	75,00%	97,45%	97,45%
Forced awakening	Yes	Y	start movement	start spikes at the same time that was marked the event	87,71%	97,06%	97,06%
Seizure	Yes	Y	start movement	electroclinical seizure. Start spikes with high amplitude and frequency	77,78%	94,79%	94,79%
Seizure	Yes	Y	start movement	start spikes after a quietness period	66,67%	98,35%	98,35%
Seizure	Yes	Y	first spike at the same time in which the clinical start was marked	clinical start lagging 17s behind EEG start	66,67%	100,00%	100,00%
Seizure	No	Y	spike with maximum amplitude		98,98%	92,36%	92,37%

Table A.5: Gross results for movement detector algorithm. Continue

Event type	Filtered	Event detected			MD		
		Y/N	Feature assessed	Comments	Sensitivity	Specificity	Accuracy
Paroxysmal	No	Y	start movement	start spikes after a quietness period	97,06%	92,80%	92,80%
Seizure	Yes	N			58,82%	99,97%	99,97%
Seizure	Yes	Y	start movement	start spikes after a quietness period	50,00%	99,92%	99,92%