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Spectral Analysis Methods for Spike-Wave Discharges in Rats with Genetic Absence Epilepsy

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1. Introduction

The WAG/Rij strain is an inbred strain of Wistar rats in which all animals present absence seizures (Coenen et al., 1992). These seizures appear as a sudden interruption of consciousness and are characterized in the cortical electroencephalogram (EEG) by the occurrence of bilateral and synchronous spike-wave discharges (SWDs) (Coenen & Van Luijtelaar, 2003).

SWDs seen in WAG/Rij rats share many clinical characteristics with typical human absence epilepsy and exhibit a similar pharmacological reactivity to drugs (Coenen et al., 1992; Van Luijtelaar & Coenen, 1986; Peeters et al., 1989). Therefore, WAG/Rij strain of rats is considered to be a valid animal model of human absence epilepsy (Ates et al., 1999; Ates et al., 2004). Nowadays this genetic model of absence epilepsy is commonly used for studying the efficacy of new antiepileptic drugs on the occurrence of SWD and the pathogenesis of absence epilepsy (Coenen & Van Luijtelaar, 2003; Bouwman & Van Rijn, 2004). However, the mechanisms underlying SWDs, still remain unclear (Bouwman et al., 2007). Although the analysis of the time–frequency (TF) structure of SWDs may contain important information about the mechanisms of this type of brain paroxysmal activity and can play a significant role in the investigation of antiepileptic drugs, the dynamics of SWDs in rodent models have been poorly investigated (Bosnyakova et al., 2006; Bosnyakova et al., 2007). It is usually indicated that in animals with absence epilepsy the typical SWDs have a mean frequency of 8.7 Hz (Van Luijtelaar & Coenen, 1986). In addition, by means of the Fast Fourier procedure it was shown that the frequency of the SWD is approximately 10-11 Hz at the beginning of and 7-8 Hz at the end of the discharges (Drinkenburg et al., 1993). Bosnyakova et.al (2006) used a modified Morlet wavelet transform to describe significant parameters of the dynamics in the TF domain of the dominant rhythm of SWD. In a recent

paper, analysis of the TF pattern of SWD in patients with absence seizures and WAG/Rij rats revealed that TF dynamics of SWDs had similar properties but in a different frequency range (Bosnyakova et al., 2007).

Spectral analysis methods can be used for representing and/or discriminating the signals recorded from WAG/Rij rats. The basic problem that we consider is the estimation of the power spectral density (PSD) of a signal from the observation of the signal over a finite time interval (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 1996; Stoica & Moses, 1997; Übeyli, 2009). The signals recorded from WAG/Rij rats are conventionally interpreted by analyzing their spectral content. Diagnosis and disease monitoring are assessed by analysis of spectral shape and parameters. In order to determine the variabilities of the signals under study are processed by spectral analysis methods to achieve PSD estimates and to obtain the features representing the signals. In the signal processing stage, numerous different methods can be used so that several diverse features can be extracted from the same raw data. The nonparametric methods (Fast Fourier transform based methods), parametric methods (model-based methods) and TF methods (wavelet transform) are the methods used for spectral analysis. The parameters obtained by these methods characterize the behaviour of the time-varying signals. This feature of using a smaller number of parameters to represent the time-varying signals is particularly important for recognition and diagnostic purposes. The objective of the chapter in the field of detection of changes in the time-varying signals is to extract the representative features of the signals under study. In this chapter, the dynamic parameters in the TF domain of SWD were analysed and results represent good additional tool for discriminating this epileptic event and new perspective for future investigations (Übeyli et al, 2008; Übeyli et al., 2009).

2. Human Absence Epilepsy: The Wag/Rij Rat as a Genetic Model

Epilepsy is a sudden and recurrent brain malfunction and is a disorder that reflects an excessive and hypersynchronous activity of the neurons within the brain. It encompasses a number of different syndromes, the cardinal feature of which is a predisposition to recurrent unprovoked seizures. It can occur at all ages, and is characterized by a variety of presentations and causes. The estimated incidence is one case per 2000 persons in the Western population per year, whereas the prevalence of active epilepsy with recent seizures is around 5–10 per 1000. For unknown reasons, the incidence of epilepsy is highest in the first year of life and increases again for those over 60 years of age. The cumulative incidence, that is, the chance of having epilepsy during a lifetime of 80 years, is about 3% (Engel et al., 2007; Fisher et al., 2005; Kwan & Sander, 2004)

By convention, the diagnosis of epilepsy requires that the patient has had at least two unprovoked seizures. Seizures are sudden, brief attacks of altered consciousness; motor, sensory, cognitive, psychic, or autonomic disturbances; or inappropriate behavior caused by abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). The phenotype of each seizure is determined by the point of origin of the hyperexcitability and its degree of spread in the brain. If given a sufficient stimulus (e.g., hypoxia, hypoglycemia), even the normal brain can discharge excessively, producing a seizure. However, a person with isolated nonrecurrent, externally provoked seizures that are also caused by excessive

discharge of cerebral neurons is not thought to have epilepsy as long as the seizures are not recurrent and each seizure is preceded by a provocation (e.g., substance abuse, fever, exposure to alcohol combined with lack of sleep) (Elger & Schmidt, 2008).
Epilepsy can also occur as a syndrome. An epileptic syndrome is an epileptic disorder characterized by a cluster of signs and symptoms occurring together; these include items such as the type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis (ILAE, 1989; Valentin et al., 2007).

Recently, epileptic seizures and epileptic syndromes is broadly divided into partial (focal or localization-related), beginning in a part of one hemisphere, and generalized, which were bilaterally symmetrical without local onset (Engel & Pedley, 2007; Weber & Lerche, 2008; Hauser et al., 1996).Partial seizures, are those in which, in general, the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere. A partial seizure is classified primarily on the basis of whether consciousness is impaired during the attack. When consciousness is not impaired, the seizure is classified as a simple partial seizure. When consciousness is impaired, the seizure is classified as a complex partial seizure where the patient is unable to respond normally to exogenous stimuli. A partial seizure may progress to a generalized motor seizure. Generalized seizures however, are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired, and this impairment may be the initial manifestation. In addition, motor manifestations are bilateral. The ictal electroencephalographic patterns initially are bilateral and presumably reflect neuronal discharge, which is widespread in both hemispheres. Generalized seizures can be classified into one of the following six fundamental groups: absence seizures, myoclonic seizures, tonic-clonic (or clonic-tonic-clonic) seizures, atonic seizures, tonic seizures, and clonic seizures. Further subdivision separates epilepsies of known etiology (symptomatic or secondary epilepsies) from those that are idiopathic (primary) and those that are cryptogenic (Weber & Lerche, 2008; Hauser et al., 1996).

Much less is known about idiopathic epilepsies. This type has no specific cause, but is assumed to have a genetic etiology. The epilepsies that are idiopathic almost always have onset childhood or adolescence, although there are exceptions: Some patients develop these kinds of epilepsies after the second decade of life, and in some rare cases, the onset may be even later. Absence, myoclonic, and tonic-clonic seizures are associated with idiopathic generalized epilepsies (IGE) (ILAE, 1989). The symptomatic epilepsies differ from the idiopathic epilepsies by having a known cause, such as head trauma, or there may be some evidence of brain or neurological dysfunction. In cryptogenic epilepsies, the etiology or side of abnormality may not be detectable or is hidden (Mattson, 2003).

One of the distinct groups of the generalized seizures is the absence seizures. Absence seizures were first described by Poupart in 1705 and, subsequently, in 1770, were called "petits accés" (petit access) by Tissot. Introduced by Calmeil (Temkin, 1994; van Luijtelaar & Sitnikova, 2006), the name "absence seizures" dates from 1824. Absence seizures are brief epileptic seizures characterized by generalized spike wave discharges (SWDs) in the cortical EEG accompanied by short falls in consciousness (absence) without the tonic-clonic

manifestations. Ongoing activity is interrupted during the seizure, responsiveness is decreased, and mental functioning is impaired. There are only minimal myoclonic jerks of the eyes and perioral automatisms. The beginning and end of the seizure are abrupt, and there is no aura or postictal state (Snead, 1995; Lockman, 1989). Depending on EEG findings absence seizures are divided into typical and atypical absence seizures (Posner et al., 2005).

The typical absence seizures are the most common and are characterized by a loss of consciousness that is time-locked with bursts of bilaterally synchronous 3 cycles/second SWDs. They are generally associated with minimal or no cognitive impairment (Snead, 1995). However, atypical absence seizures are less common, but are often associated with severe neurological impairment. Although the pharmacological profiles of the two absence types are the same, a number of features may be used to distinguish typical from atypical absence seizures (Holmes et al., 1987). One characteristic concerns voluntary behavior during the ictus (Carmant et al., 1996; Bare et al., 1998; Snead et al., 1999; Cortez et al., 2001; Nolan et al., 2005); another major difference relates to the frequency of the SWDs, both in human patients and in rodent experimental models of atypical and typical absence epilepsy (Snead, 1995; Cortez et al., 2001; Nolan et al., 2005; Velazquez et al., 2007). In addition, typical absences are brief generalized epileptic seizures with a sudden onset and termination. However, in the atypical absences seizures, the onset and termination are not as abrupt as in typical absences, and changes in tone are more pronounced (Panayiotopoulos, 2008). The usual frequency of the bilaterally synchronous SWD in typical absence seizures is 3 cycles/second, while that seen in atypical absence seizures are faster or slower than 3 cycles/second (Lockman, 1989; Snead, 1995). A third distinguishing feature is that there is a major difference in outcome between children with typical versus atypical absence seizures; atypical absence seizures are associated with a severely abnormal cognitive and neurodevelopmental outcome in children (Pavone et al., 2001; Høie et al., 2005; Henkin et al., 2005; Markand, 2003). The final distinguishing characteristic involves the neural circuitry involved in the SWD. In typical absence seizures, the epileptiform activity is constrained within thalamocortical circuitry. In addition, some evidence existing evidence indicate that while no SWD can be recorded from any circuitry other than thalamus and cortex during typical absence seizures. In contrast, there are data for the involvement of both thalamocortical and limbic circuitry in atypical absence seizures (Snead et al., 1999; Velazquez et al., 2007).

In human absence seizures, it is important to note that, typical absence seizures may be the only seizure type experienced by a child and this then constitutes either an epileptic syndrome called childhood absence epilepsy or juvenile absence epilepsy. However; absence seizures may also be only one of multiple types of seizures, as in the case of juvenile myoclonic epilepsy where myoclonic and tonic-clonic seizures occur as well as absence seizures. The Commission on Classification and Terminology of the International League Against Epilepsy recognizes four epileptic syndromes with typical AS: childhood absence epilepsy; juvenile absence epilepsy; juvenile myoclonic epilepsy and myoclonic absence epilepsy. (Posner et al., 2005; ILAE, 1989).

The annual incidence rate of absence seizures has been estimated to be 1/10,000. The estimation of the prevalence of absence seizures varies from 2.3% to 37.7%. Absence seizures

are more often seen in childhood epilepsy, and predominantly occur in children of school age; however, absence seizures also are seen in adults, albeit less commonly. A family history of epilepsy is found in 15% to 44% of patients with generalized absence seizures, and an inherited factor in human absence seizures was recognized. In addition, genetic factors play a predominant role in the etiology of IGE with typical absence seizures. Because the concordance for absence seizures in monozygotic twins does not reach 100%, acquired factors probably also play a role in this type of seizure. The mean age of onset is 7 years (range: 9 months to 12 years). Recently, the γ-aminobutyric acid (GABA) A receptor γ-2 subunit mutation has been reported to be an autosomal dominant mutation associated with childhood absence epilepsy. This mutation appears to impair GABAA receptor function (Stefan et al., 2007). The drug of choice for typical absence seizures is valproic acid or ethosuximide. In addition, absence seizures also respond well to the newer medications like lamotrigine and topiramate. However, in contrast to all other types of seizures, GABA-mimetic anti-epileptic drugs such as vigabatrin and tiagabine exacerbate absence seizures and aggravate SWDs, as predicted from outcomes in rodent models (Coenen, 1995; Cocito and Primavera, 1998; Knake et al., 1999; Depaulis & van Luijtelaar, 2006). Therefore, it is suggested that absence epilepsy is a disturbance in inhibition. (van Luijtelaar & Sitnikova, 2006). Nevertheless, pathophysiology of idiopathic generalized absence epilepsy is not fully understood (Tolmacheva et al., 2004). The benign nature of absence epilepsy precludes invasive investigation in humans; therefore, emphasis is placed on experimental animal models (acute, chronic, pharmacological, genetic, etc.) that allow the investigation of the mechanisms of pathogenesis and propose better diagnostic and therapeutic procedures of this disease.

An animal model of generalized absence seizures should, in addition to reflecting the clinical and pharmacological characteristics of this disorder, fulfill other requirements. These criteria include reproducibility and predictability, as well as the ability to standardize and quantitate the model. In addition, animal models of absence should reflect the fact that both clinical and experimental absence seizures are exacerbated by both direct and indirect GABA agonists. Finally, if an animal model of absence seizures is to be considered as a valid one, involvement of thalamocortical circuitry and specific noninvolvement of hippocampal circuitry should be demonstrated (Snead, 1995).

Although a number of pharmacological and genetic rat models meet these criteria, genetic models are the pertinent choice among the models available for human absence epilepsy. The WAG/Rij (Wistar Albino Glaxo Rijswijk) strain of rats is such a model (Snead, 1995; Coenen & van Luijtelaar, 2003).

The WAG/Rij strain is an inbred strain of rats in which brother-sister cross breeding has taken place for more than 100 generations, implying that the rats are homozygous. Therefore, rats from this strain offer an eminent possibility to study the genetic background and heredity of absence epilepsy. Furthermore, the rats are fertile and show no sings of behavioral abnormalities (Coenen et al., 1992). All individuals of this strain develop spontaneous SWDs in their EEG (van Luijtelaar & Coenen, 1986). SWDs in WAG/Rij rats are accompanied by behavioral arrest and immobility, minimal facial myoclonic jerks, twitching of eyes and vibrissae, altogether mimicking clinical manifestation of absence epilepsy in humans (WAG/Rij model has face validity). Likewise, the pharmacological profile of seizures in WAG/Rij rats and in humans is similar. This enables predictions from the model

to the patient (predictive validity of WAG/Rij model). Finally, absence seizures in WAG/Rij rats and in humans are based on the same theoretical grounds (WAG/Rij model has a construct validity). Consequently, WAG/Rij rats fulfill all the necessary criteria for a valid and reliable animal model of human absence epilepsy. (Coenen & van Luijtelaar, 2003, Sitnikova & van Luijtelaar 2006).

3. Electroencephalograms and Spike-Wave Discharges

Rhythmic electrical activity can be recorded from the cerebral cortex. This activity is known as the EEG when the activity is recorded from the surface of the skull. An EEG signal is a measurement of currents that flow during synaptic excitations of the dendrites of many pyramidal neurons in the cerebral cortex. When brain cells (neurons) are activated, the synaptic currents are produced within the dendrites. This current generates a magnetic field measurable by a secondary electrical field over the scalp measurable by EEG systems. Differences of electrical potentials are caused by summed postsynaptic graded potentials from pyramidal cells that create electrical dipoles between the soma (body of a neuron) and apical dendrites, which branch from neurons. Since the human head consists of different layers including the scalp, skull, brain, and many other thin layers in between, the skull attenuates the signals approximately one hundred times more than the soft tissue. On the other hand, most of the noise is generated either within the brain or over the scalp. Therefore, only large populations of active neurons can generate enough potential to be recordable using the scalp electrodes. These signals are later amplified greatly for display purposes (Berne & Levy, 1993; Sanei & Chambers, 2007).

The EEG is an important diagnostic tool in clinical neurology and is particularly useful in patients with epilepsy. Diagnosis of epilepsy is made primarily on patient history and neurological exam, but clinical criteria alone may not be sufficient for characterization of its type, or may not be infallible. The EEG verifies that the event in question is an epileptic seizure and not something else. It helps to classify the type of seizure and the underlying epileptic syndrome. Often, the EEG helps to pinpoint where seizures arise in the brain. The frequency of seizure occurrence and the effectiveness of therapy can be evaluated with EEG (Koutroumanidis & Smith, 2005; Berne & Levy, 1993).

Seizures characterized by paroxysmal changes of the brain's electrical activity that produce impairment in consciousness or bilateral movements; such as tonic–clonic, tonic and complex partial seizures almost always appear in the scalp EEG.

Ictal (seizure) and interictal (between seizure) EEG patterns correspond to specific seizure types and types of epilepsy. Several distinct EEG patterns appear in generalized seizures that are related to the underlying cause of the epilepsy. Seizures arising in patients with idiopathic generalized epilepsy usually begin with generalized SWDs or a burst of generalized polyspikes. Patients with symptomatic generalized epilepsy have a broader variety of ictal onset patterns, although a generalized spike and slow wave, generalized slow wave, generalized fast activity, or generalized attenuations are usually seen. Subsequent ictal EEG findings depend on the seizure type. During absence seizures, the spike-wave (S&W) pattern continues; during tonic seizures, the generalized fast activity persists. Tonic–clonic seizures display an evolving spike pattern consonant with the muscular contractions. On the other hand, absence seizures have varying characteristics. Typical absence seizures (Fig. 1) usually begin with a generalized, frontally predominant

SWD at 3.5 to 4 Hz that gradually slows to 2.5 Hz by the end of the seizure. Absence seizures often show increasing spike amplitude in the first two or three discharges. Seizure offset, while relatively quick, also often reflects a "build down," with one to three rhythmic slow waves of diminishing amplitude following the last spike discharge. There is no significant postictal slowing of the background after absence seizures. Atypical absence seizures may show somewhat more irregular S&W or polyspike and-wave discharges, sometimes at initial higher frequencies. Patients with symptomatic generalized epilepsy have atonic or tonic seizures. Atonic seizures may begin with a generalized spike or sharp wave (with or without a slow wave), a generalized slow wave, or simply a diffuse attenuation of the background EEG with or without low amplitude fast activity. In contrast, a characteristic feature of tonic seizures is the progressive buildup of generalized fast activity (15–30 Hz), which may be preceded by a S&W or a slow wave or may appear without antecedent. The seizure is usually followed by a brief period of postictal background slowing. On the other hand, during and between focal seizures, scalp recordings may reveal EEG spikes. (Sperling & Clancy, 2007).

It should be noted that seizures are infrequent events in the majority of patients, and a prolonged EEG recording session may be required to capture a seizure. Fortunately for diagnosis, 50-80% of patients with epilepsy display interictal discharges in their routine interictal EEG test. Interictal epileptiform discharges (IEDs) are more prevalent and more persistent in some epilepsy syndromes such as childhood-onset absence. In adults with partial epilepsy, IEDs are more common when seizures originate in the temporal lobes than when seizures originate elsewhere. Interictal discharges may be divided morphologically into sharp waves, spikes, S&W complexes (also called spike-and-slow-wave complexes), and polyspike-wave complexes (also called multiple-spike-and-slow-wave-complexes) (Fisher & Leppik, 2008; Worrell et al., 2002).

IEDs are difficult to describe precisely. IED must be paroxysmal and clearly distinguished from background activity. There must be an abrupt change in polarity lasting several milliseconds. Duration must be <200 milliseconds. The Committee on Terminology distinguishes between spikes, which have a duration <70 milliseconds, and sharp waves, which have a duration between 70 and 200 milliseconds. In addition, the IED must have a physiologic field. Practically, this means that the IED is recorded by more than one electrode and has a voltage gradient across the scalp. This requirement helps distinguish IEDs from artifacts. Also, focal IEDs suggest localization-related epilepsies, whereas generalized IEDs suggest generalized epilepsies (Walczak et al., 2007**)**.

The prototype of generalized epileptiform abnormalities is the sudden onset of bilaterally synchronous 2.5-4 cycles/s S&W activity. Although described as S&W activity, the morphology of the complexes is somewhat more complicated. Two spikes, a positive transient and a slow wave, make up the complex. Spike I is negative and low in amplitude (25-50 μV), short in duration, and usually not seen in the first few complexes of the burst. A positive transient lasting 100-150 ms follows spike I; this is followed by spike II which is high in amplitude (three times spike I) and lasts 30-90 ms. The slow wave following spike II is a surface negative wave, and, if one can distinguish it from the positive transient one, its duration is in the 150-250 ms range. In addition to sudden near simultaneous diffuse onset, the S&W activity phenomenon usually stops simultaneously over both hemispheres and is followed by an abrupt return of normal background activity. Potentially, the S&W activity phenomenon can be considered an aberrant age-dependent thalamocortical oscillatory

rhythm. A common assumption holds that the thalamocortical relay cells involved in spindle generation have special Ca $^{2+}$ channels called transient channels which provide them the ability to burst fire when stimulated. Also, the nucleus reticularis thalami neurons impose oscillatory behavior on the thalamocortical relay cells. Alterations seen in the nucleus reticularis thalami - thalamocortical relay -cortical neuron loop are responsible for S&W bursts (Gloor & Fariello, 1988; Snead, 1995; Schaul 1998).

WAG/Rij rats show spontaneously occurring bilaterally synchronised SWDs in the cortical EEG with a frequency of 7–11 Hz and an amplitude of 100 to 450 μV, and a mean duration of 5 seconds (1-30 seconds; Fig 2). This feature of the WAG/Rij rats allows them to be considered as a genetic animal model for typical absence seizures. SWDs in WAG/Rij rats are age-dependent. The first EEG symptoms of absence epilepsy appear in 2–3 month-old WAG/Rij rats. Later, with age, increases in the number and duration of SWDs are observed. By the age of 6 months, virtually all WAG/Rij rats show SWDs on their cortical EEGs (Coenen & Van Luijtelaar, 2003; Ilbay et al., 2001;Ates et al., 2004). SWDs do not appear randomly in time; rather, they tend to appear in clusters in rats as in humans. The amplitude of SWDs is largest in the frontal midline region and gradually decreases in the lateral and posterior directions. Onset and termination are abrupt; the attacks may be preceded and immediately followed by normal EEG activity, especially when recorded in the waking (resting) state (Kellaway, 1985; Midzyanovskaya et al., 2006; Rodin & Ancheta, 1987; van Luijtelaar & Sitnikova, 2006). Recent studies have shown that, SWDs are generated in a neuronal network involving cortical and thalamic areas in both hemispheres. The somatosensory cortex is assumed to contain the site of SWD initiation whereas, the rostral part of the reticular thalamic nucleus probably maintains SWD activity by acting as a pacemaker (Avanzini et al., 2000; Meeren et al., 2005).

4. Advanced Methods in Epileptology

Most traditional epilepsy analysis methods, based on the EEG, are focused on the detection and classification of epileptic seizures. Among these, the best method of analysis is still the visual inspection of the EEG by a highly skilled EEG specialist. Visual analysis of long term EEG records is, however, time consuming and laborious. Therefore, with the advent of new signal processing methodologies, several computerized techniques have been proposed to detect and localize epileptic seizures. Consequently, various automated spike detection approaches have been developed. Artificial neural networks (ANNs) have been used for seizure detection by many researchers. The Kohonen self-organizing feature map ANN was used for spike detection. The major problem with these methods is that the epileptic seizure signals do not follow similar patterns. Presenting all types of seizure patterns to the ANN, on the other hand, reduces the sensitivity of the overall detection system. Therefore, a clever feature detection followed by a robust classifier often provides an improved result (Sanei & Chambers, 2007).

Among recent works, TF approaches effectively use the fact that the seizure sources are localized in the TF domain. Most of these methods are mainly for detection of neural spikes of different types. Different TF methods following different classification strategies have been proposed by many researchers in this area. The methods are especially useful since the EEG signals are statistically nonstationary. The discrete wavelet transform (DWT) obtains a better TF representation than the TF based on the short-term Fourier transform due to its

multiscale (multilevel) characteristics; i.e. it can model the signal according to its coarseness. The DWT analyses the signal over different frequency bands, with different resolutions, by decomposing the signal into a coarse approximation and detail information. In a recent approach, a DWT-based TF method followed by an ANN has been suggested. The ANN classifies the energy of various resolution (detail) levels. Using this technique, it is possible to detect more than 80% of adult epileptic seizures. Other TF distributions such as the pseudo-Wigner–Ville can also be used for the same purpose (Sanei & Chambers, 2007).

Epilepsy is considered to be a dynamic disease. For this reason, it is characterized by qualitative changes from normal behavior to abnormal dynamics of some variables. Epileptic subjects display long periods of normal EEG activity intermingled occasionally with epileptiform paroxysmal activity. Thus, some measures of dynamical change have also been used for seizure detection. These measures significantly change in the transition between the preictal and ictal states or even in the transition between the interictal and ictal states (Suffczynski et al., 2006; Sanei & Chambers, 2007).

The mechanisms of epileptogenesis -the transformation of a naive network to one that generates seizures- are poorly understood (Khalilov et al., 2005). One of the classical ways to study epileptogenesis is by studying clinical and electroencephalographic characteristics. Modern approaches utilize advanced methods such as computational models that are based on neuroanatomical and electrophysiological properties of the circuitry that is involved in the development of SWDs (van Luijtelaar, et al., 2004). Wladimir Yakhno and colleagues demonstrated that normal and pathological oscillations may emerge in the same sensory network and that changes in the degree of interdependence among the distributed neuron ensembles, constituting of the reticular thalamic nucleus, the thalamic relay nuclei and the cortex, gives rise to various models of operandi of neural firing patterns similar to normal firing as well as to SWDs (Yakhno et al., 2004).

Nowadays, genetic absence epilepsy rodent model is commonly used for studying spectral and TF analysis of SWD patterns under various physiological and pharmacological drug conditions, automatic seizure detection, and seizure prediction. Inna Midzyanovskaya from the Institute of Higher Nervous Activity in close collaboration with Vasely Strelkov analysed long-term EEG records of WAG/Rij rats. They reported in their article the general parameters of S&W activity and its spectral characteristics. They found various types of regularities: a strong modulation with a period length of 24-hours, as well as modulations with period lengths ranging from a few minutes to several hours. Their analyses of the intervals between two successive periods with SWDs also revealed a weak rhythm, with an interval of 3-6 seconds, corresponding to a frequency of 0.17 to 0.33 Hz (Midzyanovskaya, et al., 2006).

Wavelet transforms provide information about the time and the frequency structures of a signal simultaneously. For the investigation of dynamic characteristics of SWDs characterizing absence epilepsy during physiological conditions and after the administration of a drug, Bosnyakova et al., used the wavelet transform. This allowed the researcher to observe that the periodical SWD amplitude changes in the range from tenths of a second to one second, as well as the SWDs frequency from the beginning to the end of the discharge. The results of this work also demonstrated the usefulness of applying wavelet transforms for TF analysis of SWD patterns under various pharmacological drug conditions, addressing different brain mediator systems (Bosnyakova, et al., 2006).

In an established work by Tel'nykh et al., an algorithm has been proposed for detecting SWDs, sleep spindles and other characteristic phasic events in the EEG recorded from the cortical and subcortical structures in WAG/Rij rats. The program is capable for recording, analyzing, and automatic finding of characteristic features in the EEG (Tel'nykh et al., 2004).
In addition, based on the mathematical theory of nonlinear dynamics, there has been an increased interest in the analysis of the EEG for the prediction of epileptic seizures. It has been shown that epileptic sources gradually tend to be less chaotic from a few minutes before the seizure onset. This finding is clinically very important since it indicates that the patients do not need to be under anticonvulsant administration permanently, but from just a few minutes before seizure (Sanei & Chambers, 2007).
In terms of genetic absence epilepsy rats and human patients, SWDs emerge suddenly from a normal background EEG and do not seem to be anticipated by any peculiar EEG changes. This gives the impression that S&W seizures are "suddenly generalized". The common definition of S&W seizures, given as suddenly generalized and bilaterally synchronous activities, may be valid at the macroscopic EEG level. However; forerunners of S&W seizures are almost invisible on macroscopic EEG level, although neuronal activity has definitely been changed before the seizure onset. In fact, cortical neurons display time lags between their rhythmic spike trains and progressively increased synchrony. These neuronal processes may involve subtle EEG changes that cannot be easily seen in EEG, but can be detected and validated with methods of mathematical analysis of digitally recorded EEG signal. Unfortunately, only few studies have reported EEG changes during transitional state between background activity and S&W seizures (Pinault et al., 2001; Inouye et al., 1990; Steriade & Amzica, 1994; van Luijtelaar & Sitnikova, 2006).

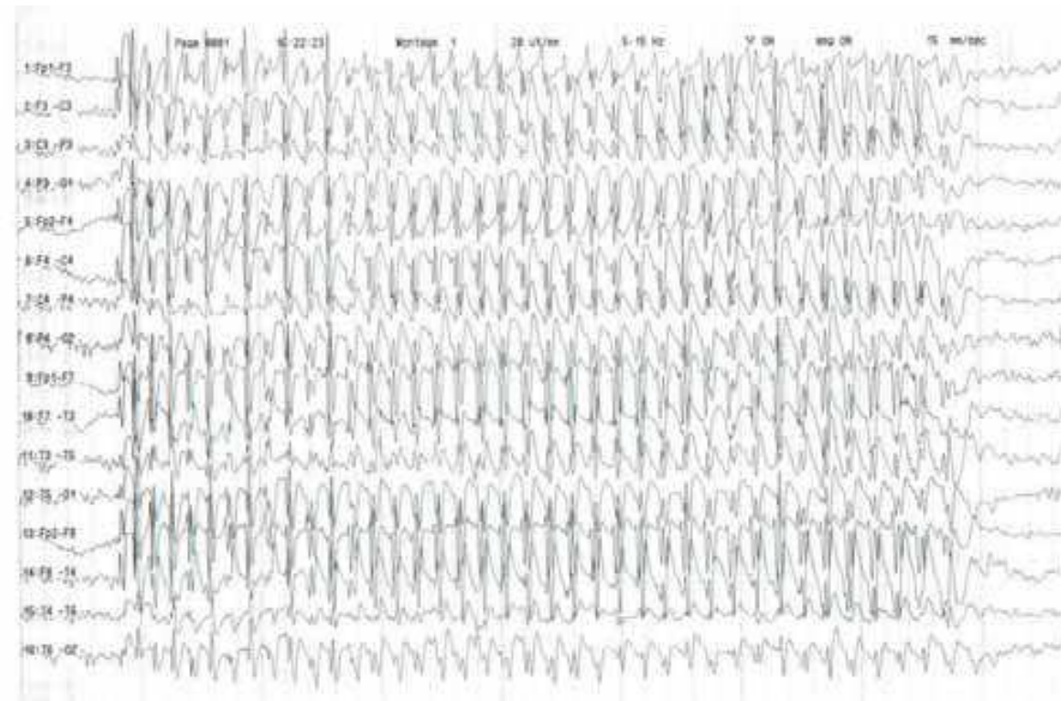


Fig. 1. EEG recording of an absence seizure showing the spike-wave discharges.

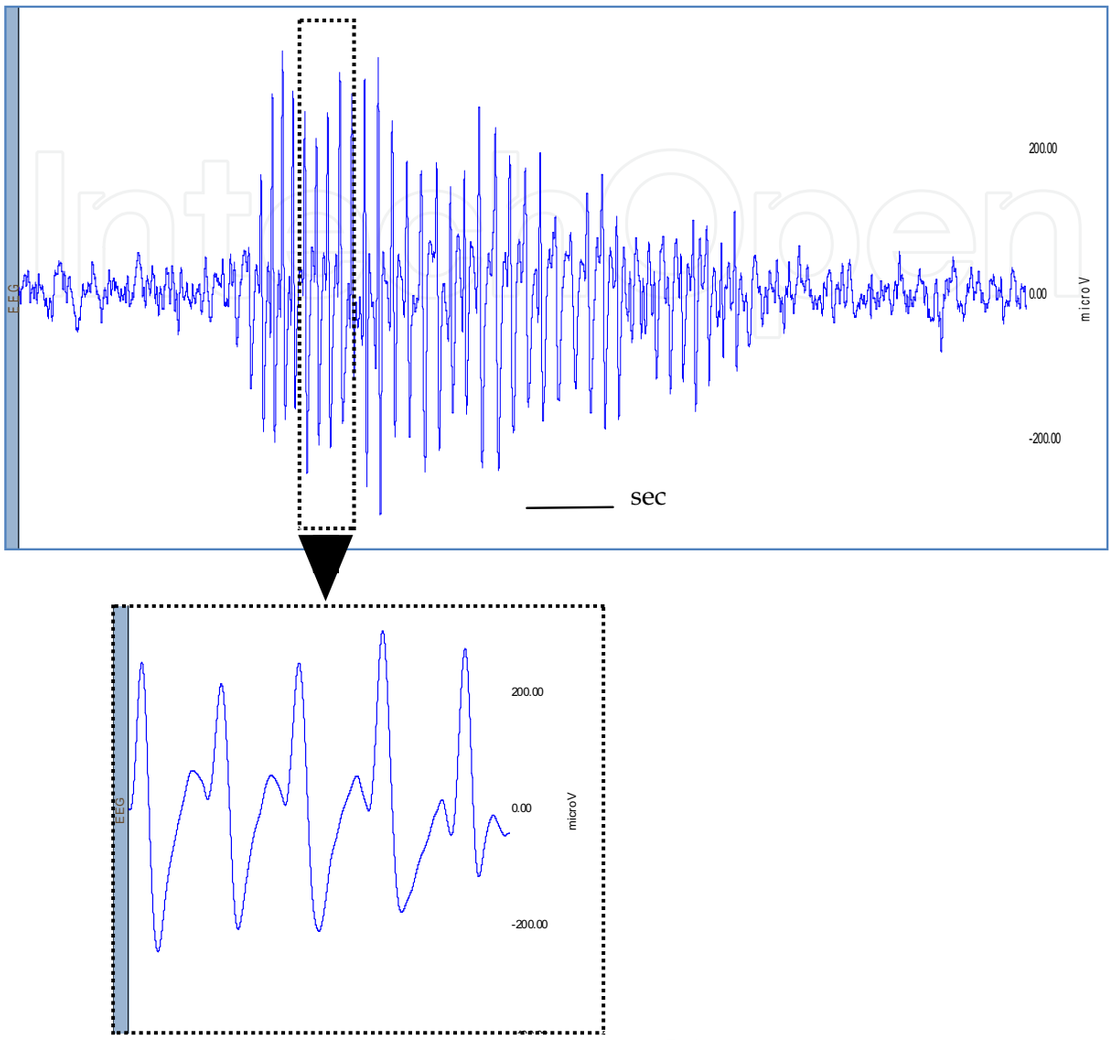


Fig 2. Representative spike-wave discharges in the EEG of a WAG/Rij rat.

5. Spectral Analysis Methods for Spike-Wave Discharges

In order to achieve PSD estimates which represent the changes in frequency with respect to time and to obtain the features, the classical methods (nonparametric or fast Fourier transform-based methods), model-based methods (autoregressive, moving average, and autoregressive moving average methods), TF methods (wavelet transform) are presented in the following.

5.1 Nonparametric methods

The nonparametric methods of spectral estimation rely entirely on the definitions of the equations (1) and (2) of PSD to provide spectral estimates. These methods constitute the "classical means" for PSD estimation. We first introduce two common spectral estimators,

the periodogram and the correlogram derived directly from equations (1) and (2), respectively.

$$P(f) = \lim_{N\to\infty} E\left\{\frac{1}{N}\left|\sum_{n=1}^{N} x(n)e^{-j2\pi f}\right|^2\right\} \tag{1}$$

$$P(f) = \sum_{k=-\infty}^{\infty} r(k)e^{-j2\pi fk} \tag{2}$$

where $P(f)$ is power spectral density and $r(k)$ is autocorrelation function of the signal under study.

These methods are equivalent under weak conditions. The periodogram and correlogram methods provide reasonably high resolution for sufficiently long data lengths, but are poor spectral estimators because their variance is high and does not decrease with increasing data length. The high variance of the periodogram and correlogram methods motivates the development of modified methods that have lower variance, at a cost of reduced resolution. The modified power spectrum estimation methods described in this section are developed by Bartlett (1948), Blackman and Tukey (1958), and Welch (1967) (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997). These methods make no assumption about how the data were generated and hence are called nonparametric. The spectral estimates are expressed as a function of the continuous frequency variable f, in practice, the estimates are computed at discrete frequencies via the fast Fourier transform (FFT) algorithm.

5.2 Parametric methods

The parametric or model-based methods of spectral estimation assume that the signal satisfies a generating model with known functional form, and then proceed by estimating the parameters in the assumed model. The signal's spectral characteristics of interest are then derived from the estimated model. The models to be discussed are the time series or rational transfer function models. They are the autoregressive (AR) model, the moving average (MA) model, and the autoregressive-moving average (ARMA) model. The AR model is suitable for representing spectra with narrow peaks. The MA model provides a good approximation for those spectra which are characterized by broad peaks and sharp nulls. Such spectra are encountered less frequently in applications than narrowband spectra, so there is a somewhat limited interest in using the MA model for spectral estimation. For this reason, our discussion of the MA spectral estimation will be brief. Spectra with both sharp peaks and deep nulls can be modeled by ARMA model. However, the great initial promise of ARMA spectral estimation diminishes to some extent because there is yet no well-established algorithm, from both theoretical and practical standpoints, for ARMA parameter estimation. The theoretically optimal ARMA estimators are based on iterative procedures whose global convergence is not guaranteed. The practical ARMA estimators are computationally simple and often quite reliable, but their statistical accuracy may be poor in some cases (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997).

5.2.1 AR method

AR method is the most frequently used parametric method because estimation of the AR parameters can be done easily by solving linear equations. In the AR method, data can be modeled as output of a causal, all-pole, discrete filter whose input is white noise. The AR method of order p is expressed as the following equation:

$$x(n) = -\sum_{k=1}^{p} a(k)x(n-k) + w(n), \tag{3}$$

where $a(k)$ are the AR coefficients and $w(n)$ is white noise of variance equal to σ^2. The AR (p) model can be characterized by the AR parameters $\{a[1], a[2], \ldots, a[p], \sigma^2\}$. The PSD is

$$P_{AR}(f) = \frac{\sigma^2}{|A(f)|^2}, \tag{4}$$

where $A(f) = 1 + a_1 e^{-j2\pi f} + \ldots + a_p e^{-j2\pi fp}$.

To obtain stable and high performance AR method, some factors must be taken into consideration such as selection of the optimum estimation method, selection of the model order, the length of the signal which will be modeled, and the level of stationary of the data (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997).

Because of the good performance of the AR spectral estimation methods as well as the computational efficiency, many of the estimation methods to be described are widely used in practice. The AR spectral estimation methods are based on estimation of either the AR parameters or the reflection coefficients. Except the maximum likelihood estimation, the techniques estimate the parameters by minimizing an estimate of the prediction error power. The maximum likelihood estimation method is based on maximizing the likelihood function (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997).

5.2.2 MA method

The MA method is one of the model-based methods in which the signal is obtained by filtering white noise with an all-zero filter. Estimation of the MA spectrum can be done by the reparameterization of the PSD in terms of the autocorrelation function. The q th-order MA PSD estimation is (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997)

$$\hat{P}_{MA}(f) = \sum_{k=-q}^{q} \hat{r}(k)e^{-j2\pi fk}. \tag{5}$$

5.2.3 ARMA method

The spectral factorization problem associated with a rational PSD has multiple solutions, with the stable and minimum phase ARMA model being one of the model-based methods. A reliable method is to construct a set of linear equations and to use the method of least squares on the set of equations. Suppose that for an ARMA of order p, q the autocorrelation

sequence can be accurately estimated up to lag M, where $M > p+q$. Then the following set of linear equations can be written:

$$\begin{bmatrix} r(q) & r(q-1) & \cdots & r(q-p+1) \\ r(q+1) & r(q) & \cdots & r(q-p+2) \\ \vdots & \vdots & & \\ r(M-1) & r(M-2) & & r(M-p) \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ \vdots \\ a_p \end{bmatrix} = -\begin{bmatrix} r(q+1) \\ r(q+2) \\ \vdots \\ r(M) \end{bmatrix}, \tag{6}$$

or equivalently,

$$Ra = -r. \tag{7}$$

Since dimension of R is $(M-q)xp$ and $M-q > p$ the least squares criterion can be used to solve for the parameter vector a. The result of this minimization is

$$\hat{a} = -\left(R^* R\right)^{-1}\left(R^* r\right). \tag{8}$$

Finally the estimated ARMA power spectrum is (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997)

$$\hat{P}_{ARMA}(f) = \frac{\hat{P}_{MA}(f)}{\left|1 + \sum_{k=1}^{p} \hat{a}(k) e^{-j2\pi fk}\right|^2}, \tag{9}$$

where $\hat{P}_{MA}(f)$ is estimate of the MA PSD and is given in equation (5).

5.2.4 Selection of AR, MA, ARMA model orders

One of the most important aspects of the use in model-based methods is the selection of the model order. Much work has been done by various investigators on this problem and many experimental results have been given in the literature (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 2007; Stoica & Moses, 1997). One of the better known criteria for selecting the model order has been proposed by Akaike (1974), called the Akaike information criterion (AIC), is based on selecting the order that minimizes equation (10) for the AR method, equation (11) for the MA method, and equation (12) for the ARMA method:

$$AIC(p) = \ln \hat{\sigma}^2 + 2p/N, \tag{10}$$

$$AIC(q) = \ln \hat{\sigma}^2 + 2q/N, \tag{11}$$

$$AIC(p,q) = \ln \hat{\sigma}^2 + 2(p+q)/N, \tag{12}$$

where $\hat{\sigma}^2$ is the estimated variance of the linear prediction error.

5.3 Wavelet Transform

The WT is designed to address the problem of nonstationary signals. It involves representing a time function in terms of simple, fixed building blocks, termed wavelets. These building blocks are actually a family of functions which are derived from a single generating function called the mother wavelet by translation and dilation operations. Dilation, also known as scaling, compresses or stretches the mother wavelet and translation

shifts it along the time axis (Akay, 1998; Daubechies, 1990; Unser & Aldroubi, 1996; Mallat, 1998; Soltani, 2002; Übeyli, 2008).

The WT can be categorized into continuous and discrete. Continuous wavelet transform (CWT) is defined by

$$\mathrm{CWT}(a,b) = \int_{-\infty}^{+\infty} x(t)\psi_{a,b}^{*}(t)dt \,, \tag{13}$$

where $x(t)$ represents the analyzed signal, a and b represent the scaling factor (dilatation/compression coefficient) and translation along the time axis (shifting coefficient), respectively, and the superscript asterisk denotes the complex conjugation. $\psi_{a,b}(\cdot)$ is obtained by scaling the wavelet at time b and scale a :

$$\psi_{a,b}(t) = \frac{1}{\sqrt{|a|}}\psi\left(\frac{t-b}{a}\right) , \tag{14}$$

where $\psi(t)$ represents the wavelet.

Continuous, in the context of the WT, implies that the scaling and translation parameters a and b change continuously. However, calculating wavelet coefficients for every possible scale can represent a considerable effort and result in a vast amount of data. Therefore DWT is often used. The WT can be thought of as an extension of the classic Fourier transform, except that, instead of working on a single scale (time or frequency), it works on a multi-scale basis. This multi-scale feature of the WT allows the decomposition of a signal into a number of scales, each scale representing a particular coarseness of the signal under study. In the procedure of multiresolution decomposition of a signal $x[n]$, each stage consists of two digital filters and two downsamplers by 2. The first filter, $g[\cdot]$ is the discrete mother wavelet, high-pass in nature, and the second, $h[\cdot]$ is its mirror version, low-pass in nature. The downsampled outputs of first high-pass and low-pass filters provide the detail, D_1 and the approximation, A_1, respectively. The first approximation, A_1 is further decomposed and this process is continued (Akay, 1998; Daubechies, 1990; Unser & Aldroubi, 1996; Mallat, 1998; Soltani, 2002; Übeyli, 2008).

6. Results of Analysis

The PSDs describe the distribution of power with frequency. In this study, the PSDs of the SWDs of WAG/Rij rats were obtained by using the FFT, Burg AR, MA, and least squares modified Yule-Walker ARMA methods. The sample PSDs of the SWD records of WAG/Rij rats are presented in Figures 3 and 4. When the PSDs are examined, it is seen that classical method (FFT) has large variance (Figures 3 and 4). The FFT method is based on a finite record of data, the frequency resolution of these methods equal to the spectral width of the window length N, which is approximately $1/N$. The principal effect of windowing that occurs when processing with the FFT is to smear or smooth the estimated spectrum. This method suffers from spectral leakage effects, due to windowing that are inherent in finite-length data records. Often, the spectral leakage masks weak signals that are present in the

data. Smearing and spectral leakage are particularly critical for spectra with large amplitude ranges, such as peaky spectra.

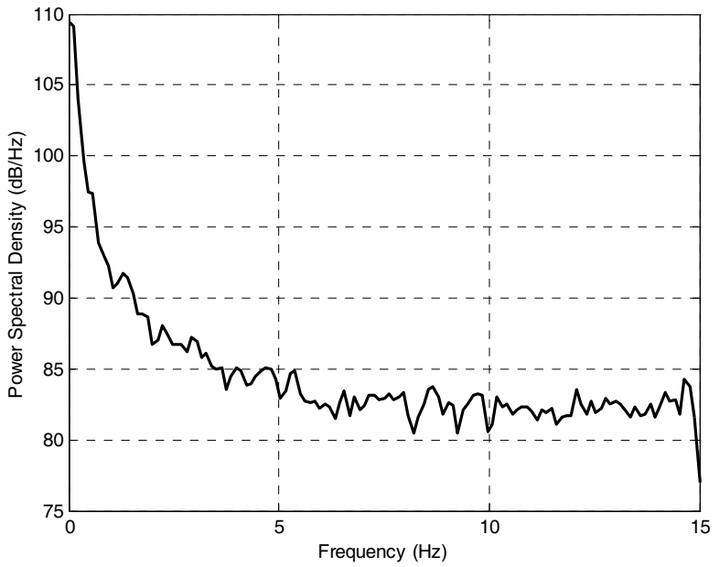


Fig. 3. PSD of sample SWD recods obtained by FFT method

A model for the signal generation can be constructed with a number of parameters that can be estimated from the observed data. From the model and the estimated parameters, the PSD can be computed. The modeling approach eliminates the need for window functions and the assumption that the autocorrelation sequence is zero outside the window. Spectra with both sharp peaks and deep nulls cannot be modeled by either AR or MA methods. In these cases, the ARMA spectral estimation provides an opportunity to improve on the AR and MA spectral estimations. By combining poles and zeros, the ARMA method provides a more efficient representation, from the viewpoint of the number of model parameters, of the spectrum of a random process. When the PSDs are examined, the Burg AR and the least squares modified Yule-Walker ARMA methods' performance characteristics have been found to be superior to the FFT and the MA methods.

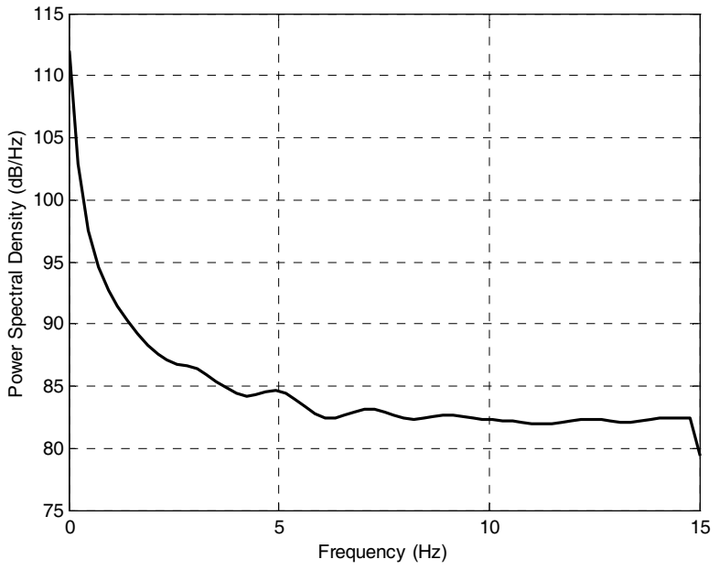


Fig. 4. PSD of sample SWD recods obtained by ARMA method

The selection of the model orders in the AR, MA, and ARMA spectral estimators is a critical subject. Too low order results in a smoothed estimate, while too large order causes spurious peaks and general statistical instability. In the case of the dimension of autocorrelation matrix is inappropriate and the model orders chosen incorrect, poor spectral estimates are obtained by the AR, MA, and ARMA spectral estimators. Heavy biases and/or large variabilities may be exhibited. In this study, Akaike Information Criteria (Akaike, 1974) was taken as the base for choosing the model order. According to the equations (10), (11), and (12) model order p was taken as 10 for the AR method, model order q was taken as 10 for the MA method and model orders p and q were taken as 10 for the ARMA method.

The mean values of the peak frequencies and power levels of the PSDs of all SWD records of WAG/Rij rats are given in Table 1. According to the values presented in Table 1, the PSD of the FFT method has spurious peaks and does not produce accurate spectral estimates due to limits on resolution. Since the PSD of the SWD records obtained by the MA method is smooth, the MA method has been found inappropriate for the SWDs. The peak frequencies and power levels of the AR and ARMA methods are similar for the PSDs of the SWDs of WAG/Rij rats. The AR and the ARMA methods produce frequency estimates which are unbiased and nearly attain the Cramer-Rao bound. From Table 1, one can see that the AR and the ARMA methods produce the true frequencies as the peaks of the spectral estimates for the SWDs. The obtained results demonstrated that the peak frequencies and the power levels of the AR and ARMA PSDs can be used as the features representing the SWD records of WAG/Rij rats.

Method	P_1 / f_1	P_2 / f_2	P_3 / f_3	P_4 / f_4
FFT	Spurious peaks			
AR	113.1706/0	85.0981/4.9219	82.8657/7.2656	83.0971/14.2969
MA	110.8564/0	–	–	81.4569/14.7656
ARMA	111.8974/0	85.5421/4.9219	82.8964/7.2656	81.8633/14.2969

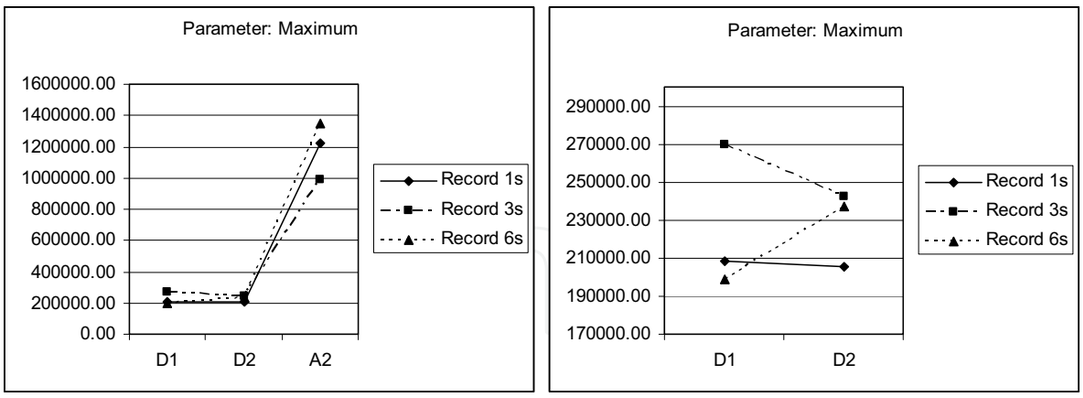
Table 1. Mean values of peak frequencies and power levels of PSDs of all SWD recods

The spectral analysis of the SWDs of WAG/Rij rats was performed using the DWT. The selection of appropriate wavelet and the number of decomposition levels is very important in analysis of signals using the DWT. The number of decomposition levels is chosen based on the dominant frequency components of the signal. The levels are chosen such that those parts of the signal that correlate well with the frequencies required for classification of the signal are retained in the wavelet coefficients. In the present study, the number of decomposition levels was chosen to be 2. Thus, the SWD records were decomposed into the details $D_1 - D_2$ and one final approximation, A_2. Usually, tests are performed with different types of wavelets and the one which gives maximum efficiency is selected for the particular application. The smoothing feature of the Daubechies wavelet of order 2 (db2) made it more suitable to detect changes of the signals under study. Therefore, the wavelet coefficients were computed using the db2 in the present study. The frequency bands corresponding to different levels of decomposition for db2 with a sampling frequency of 60 Hz are: D_1 (7.5-15Hz); D_2 (3.75-7.5Hz); and A_2 (0-3.75Hz). The wavelet coefficients were computed using the MATLAB software tool (Übeyli et al., 2008; Übeyli et al., 2009).

The computed wavelet coefficients provide a compact representation that shows the energy distribution of the signal in time and frequency. Therefore, the computed wavelet coefficients of the SWD records for each WAG/Rij rats were used as the feature vectors representing the signals. In order to reduce the dimensionality of the extracted feature vectors, statistics over the set of the wavelet coefficients was used. The following statistical features were used to represent the TF distribution of the signals under study:

1. Maximum of the wavelet coefficients in each subband.
2. Mean of the wavelet coefficients in each subband.
3. Minimum of the wavelet coefficients in each subband.
4. Standard deviation of the wavelet coefficients in each subband.

68 typical SWDs (length 4-8s) obtained from 8 WAG/Rij rats were analyzed. The wavelet coefficients of 1s, 3s and 6s were computed for each SWD. Figure 5 demonstrates the maximum, mean, minimum and standard deviation of the wavelet coefficients in each subband (D_1, D_2, A_2) of the SWD records obtained from the 1st WAG/Rij rat for 1s, 3s and 6s. From Figure 5, one can see that the computed features (wavelet coefficients in each subband) of the SWD records of WAG/Rij rats in various seconds are different from each other. This figure indicated that the wavelet coefficients can be used to identify characteristics of the SWD records of WAG/Rij rats that were not apparent from the original time domain signal (Übeyli et al., 2008; Übeyli et al., 2009).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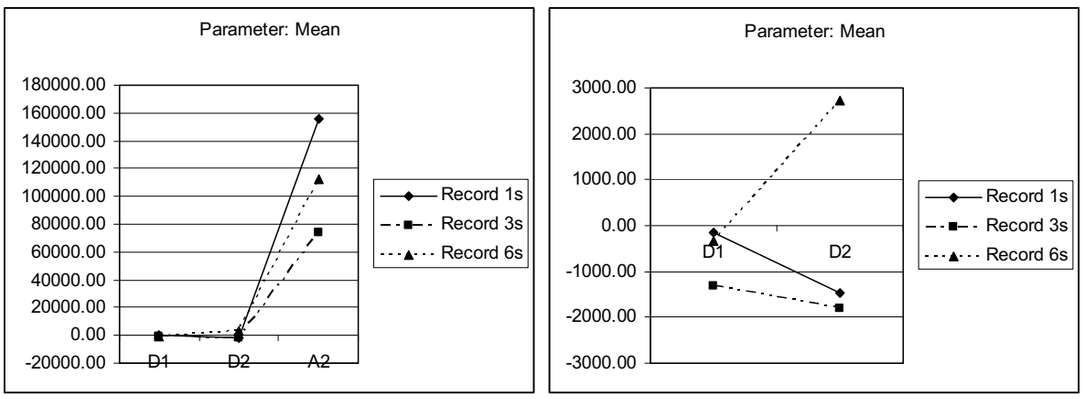
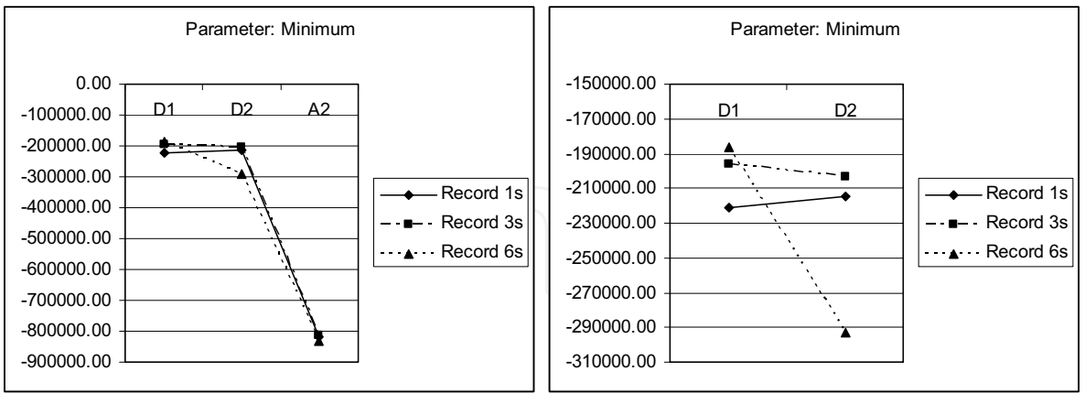
1400000.00
1200000.00
1000000.00
800000.00
600000.00
400000.00
200000.00
0.00
D1
D2
A2
Record 1s
Record 3s
Record 6s
Parameter: Maximum
290000.00
270000.00
250000.00
230000.00
210000.00
190000.00
170000.00
D1
D2
Record 1s
Record 3s
Record 6s

(a)


Parameter: Mean
180000.00
160000.00
140000.00
120000.00
100000.00
80000.00
60000.00
40000.00
20000.00
0.00
-20000.00
D1
D2
A2
Record 1s
Record 3s
Record 6s
Parameter: Mean
3000.00
2000.00
1000.00
0.00
-1000.00
-2000.00
-3000.00
D1
D2
Record 1s
Record 3s
Record 6s

(b)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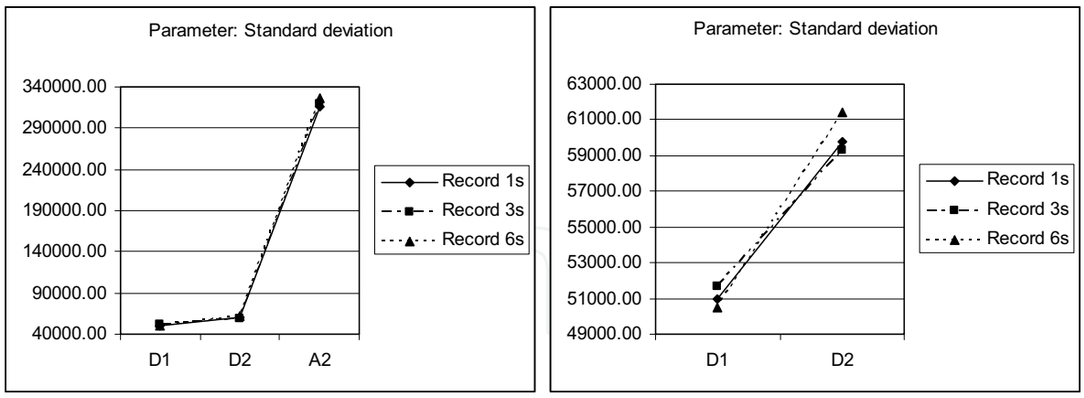
-100000.00
-200000.00
-300000.00
-400000.00
-500000.00
-600000.00
-700000.00
-800000.00
-900000.00
D1
D2
A2
Record 1s
Record 3s
Record 6s
Parameter: Minimum
-150000.00
-170000.00
-190000.00
-210000.00
-230000.00
-250000.00
-270000.00
-290000.00
-310000.00
D1
D2
Record 1s
Record 3s
Record 6s

(c)



(d)

Fig. 5. Analysis results of SWD records of WAG/Rij rat 1

7. Conclusion

In this chapter, promising results in detecting the changes in the SWD records of WAG/Rij rats were presented. The SWD records of WAG/Rij rats were processed using the FFT, Burg AR, MA, and least squares modified Yule-Walker ARMA methods. Performance of these methods were compared in terms of their frequency resolution and the effects in clinical applications. Since the FFT and the MA methods have low spectral resolution, these two methods have not been found appropriate for evaluating the PSDs of the SWD records of WAG/Rij rats. The performance characteristics of the Burg AR and the least squares modified Yule-Walker ARMA methods have been found extremely valuable for analysis of the SWD records, because of their clear spectra. In conclusion, it should be emphasized that the AR and ARMA methods were found extremely valuable for extraction of the features representing the SWD records of WAG/Rij rats.

The features from the SWD records of WAG/Rij rats were obtained by usage of the DWT. The computed wavelet coefficients can be used as features representing and/or discriminating the SWD records of WAG/Rij rats in various seconds. The results showed that the DWT can be useful to analyze TF dynamics of SWDs both in physiological conditions and after pharmacological interventions for future investigations.

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Recent Advances in Biomedical Engineering

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The field of biomedical engineering has expanded markedly in the past ten years. This growth is supported by advances in biological science, which have created new opportunities for development of tools for diagnosis and therapy for human disease. The discipline focuses both on development of new biomaterials, analytical methodologies and on the application of concepts drawn from engineering, computing, mathematics, chemical and physical sciences to advance biomedical knowledge while improving the effectiveness and delivery of clinical medicine. Biomedical engineering now encompasses a range of fields of specialization including bioinstrumentation, bioimaging, biomechanics, biomaterials, and biomolecular engineering. Biomedical engineering covers recent advances in the growing field of biomedical technology, instrumentation, and administration. Contributions focus on theoretical and practical problems associated with the development of medical technology; the introduction of new engineering methods into public health; hospitals and patient care; the improvement of diagnosis and therapy; and biomedical information storage and retrieval. The book is directed at engineering students in their final year of undergraduate studies or in their graduate studies. Most undergraduate students majoring in biomedical engineering are faced with a decision, early in their program of study, regarding the field in which they would like to specialize. Each chosen specialty has a specific set of course requirements and is supplemented by wise selection of elective and supporting coursework. Also, many young students of biomedical engineering use independent research projects as a source of inspiration and preparation but have difficulty identifying research areas that are right for them. Therefore, a second goal of this book is to link knowledge of basic science and engineering to fields of specialization and current research. The editor would like to thank the authors, who have committed so much effort to the publication of this work.

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