journal homepage: www.intl.elsevierhealth.com/journals/cmpb

An algorithm for on-line detection of high frequency oscillations related to epilepsy

Armando López-Cuevas[a,*], *Bernardino Castillo-Toledo*[a,1], *Laura Medina-Ceja*[b,2], *Consuelo Ventura-Mejía*[b,2], *Kenia Pardo-Peña*[b,2]

[a] *Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV), Unidad Guadalajara, Av. del Bosque 1145, col. El bajío, C.P. 45019, Zapopan, Jalisco, Mexico*

[b] *Laboratorio de Neurofisiología y Neuroquímica, Departamento de Biología Celular y Molecular, CUCBA, Universidad de Guadalajara, Mexico*

ARTICLE INFO

Article history:
Received 28 March 2012
Received in revised form
18 December 2012
Accepted 30 January 2013

Keywords:
Epilepsy
Fast ripples
High frequency oscillations
Approximate entropy
Cubature Kalman Filter

ABSTRACT

Recent studies suggest that the appearance of signals with high frequency oscillations components in specific regions of the brain is related to the incidence of epilepsy. These oscillations are in general small in amplitude and short in duration, making them difficult to identify. The analysis of these oscillations are particularly important in epilepsy and their study could lead to the development of better medical treatments. Therefore, the development of algorithms for detection of these high frequency oscillations is of great importance.

In this work, a new algorithm for automatic detection of high frequency oscillations is presented. This algorithm uses approximate entropy and artificial neural networks to extract features in order to detect and classify high frequency components in electrophysiological signals. In contrast to the existing algorithms, the one proposed here is fast and accurate, and can be implemented on-line, thus reducing the time employed to analyze the experimental electrophysiological signals.

1. Introduction

The electrical activity in the brain is a highly complex phenomenon. Signals may present frequency components in a broad spectrum, ranging from 1 to 500 Hz [1,2] or even higher [3]. Frequencies in the lower ranges (1–30 Hz) can be detected at the scalp as EEG fluctuations [4]. Usually these low frequency oscillations are categorized on different sub-bands: slow oscillation (<1 Hz), Delta (2–4 Hz), Theta (4–12 Hz), Alpha (9–13 Hz) and Beta (10–30 Hz), and their association to particular brain states are to date well documented [5,6]. Recent studies have focused on a higher band of frequencies in the range of 100–500 Hz. Such oscillations are local field potentials and are more easily recorded with intracerebral microelectrodes. This activity occurs at the beginning and during the epileptogenesis [7,8], and it has been suggested that some high frequency oscillations (HFO) in hippocampus are biomarkers of epileptogenic zones [9] and could be useful in predicting seizures. However, HFO detection is complicated and time-consuming due to their short duration and small amplitude. Most studies of HFO are carried out by visual inspection but this is a cumbersome task specially for long time recordings with several microelectrodes. Some algorithms for automatic

* *Corresponding author*. Tel.: +52 33 37773600; fax: +52 33 37773609.
E-mail address: acuevas@gdl.cinvestav.mx (A. López-Cuevas).
[1] Tel.: +52 33 37773600.
[2] Tel.: +52 33 37771191x33201.

0169-2607/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cmpb.2013.01.014

detection of this activity have been developed [10,11], although they are implemented off-line. These algorithms are based on energy and statistical measures that need to be calculated over the entire signal duration. To overcome some of these drawbacks, in this paper we propose an algorithm for the detection of HFO, which is able to be implemented on-line. This approach has several advantages: it is fast, accurate and it is designed for real-time detection of HFO.

2. High frequency oscillations related to epilepsy

In hippocampus, HFO in the range of 100–200 Hz, commonly known as Ripples, are believed to play an important role in memory consolidation, acting as compression waves during non-REM sleep [12,13]. Oscillations at higher ranges of frequencies (250–500 Hz) are named fast ripples and they are related to pathological conditions of the brain [14]. Ripples and fast ripples have been the object of several studies over the past years both in experimental models [15,16] and in human studies [17,18]. Particular interest in the HFO has increased in neuroscience research, mainly because most neurons do not fire at high frequencies, due to their refractory period (i.e. the elapsed time after a neuron fires an action potential until the neuron is able to fire again) and other intrinsic properties. Thus, further research need to be done in order to understand how such oscillations are generated. Interestingly, there is an increasing evidence that in specific regions of the brain where the fast ripples are detected, they are related to the development of epilepsy as well to the onset of epileptic seizures [19,20]. Specifically, the HFO called ripples can be observed in hippocampal areas of epileptic animals where they never occur under normal conditions [21]. Typical HFO superimposed on a slower wave recorded in the hippocampus of an epileptic rat occur during the interictal period (i.e. the period between two seizures) and at the onset of seizures. Thus it has been suggested that accurately real time detection of HFO could help to predict an incoming seizure condition [22]. The mechanisms underlying these oscillations are still under discussion. Several hypothesis have been proposed but still none fully confirmed. One hypothesis is that interneurons from hippocampus produce these HFO because they are capable of firing at high rates; nevertheless several studies have shown that the interneurons fire sparsely during HFO [23].

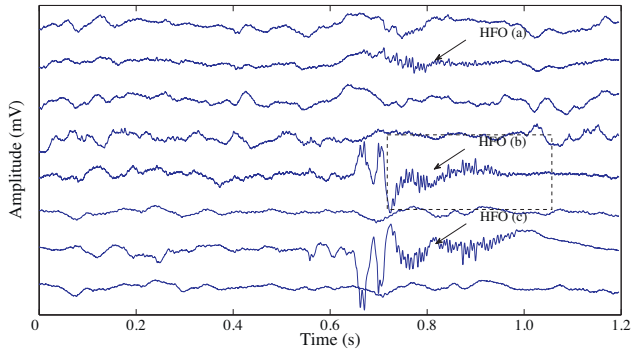

Fig. 1 – Typical occurrence of HFO in electrophysiological signals.

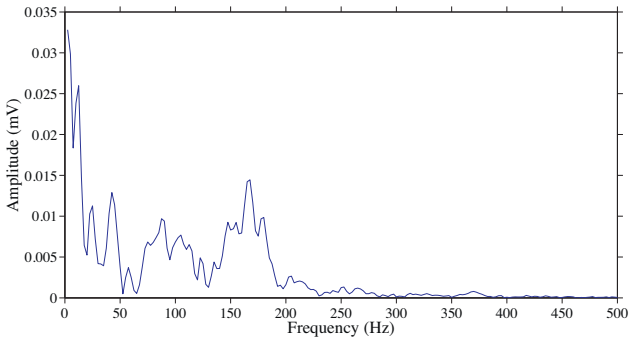

Fig. 2 – Frequency spectrum of the HFO B (detail).

Besides, in vitro studies have shown that HFO can exist even with blockade of chemical synapses [24]. This evidence supports the hypothesis that non-synaptical mechanisms could be responsible for generating HFO, perhaps ephaptic interactions or electrical coupling between axons of principal cells [25]. This type of electrical coupling has been shown to exists among mossy fiber axons in hippocampus [26]. Fig. 1 shows the occurrence of a typical HFO signal and Fig. 2 shows the frequency spectrum of the signal depicted inside the dashed box in Fig. 1.

3. Experimental methods

In this work, five Wistar rats (250 ± 30 g weight, males) were injected with pilocarpine (9.8 μmol, 1 μL/min during 2 min) via intracerebral-ventricular in order to induce a *status epilepticus* and eventually spontaneous recurrent seizures. Pilocarpine is a muscarinic agonist used to reproduce several characteristics of human temporal lobe epilepsy. This experimental model was chosen because the presence of HFO similar to those present in humans with epilepsy has been observed [23]. After 90 min of status epilepticus the rats were treated with diazepam to reduce mortality. The rats were video-monitored during two weeks every month until the presence of spontaneous recurrent seizures. Later, eight intracerebral microelectrodes were implanted bilaterally in the dentate gyrus (DG) and CA1 regions of hippocampal formation of the five rats (DG: AP −3.5 mm, ML ±2.0 mm from bregma, DV −4.0 mm from the surface of neocortex; CA1: AP −5.0 mm, ML ±5.0 mm from bregma, DV −5.5 mm from the surface of neocortex). Each microelectrode was connected to a polygraph with eight amplifiers (Grass Technologies, Inc., RI, USA) to amplify the signal. Then, the amplified signal was filtered (lowpass 10 kHz filter and high pass 0.1 Hz filter) and digitized with a 12-bit precision data acquisition system MP150 (BIOPAC systems, CA, USA) with a sampling rate of 5 kHz. A pair of microelectrodes were implanted in the right angular bundle to stimulate perforant path afferents to the hippocampus (AP −7.0 mm, ML 3.5 mm from bregma, DV 2.5 mm from the surface of neocortex). The stimulation signal was a electrical pulse with a duration of 0.1 ms and 0.1–1.0 mA in amplitude; the pulse was applied every 10 s.