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Cluster-based spike detection algorithm adapts to interpatient and inpatient variation in spike morphology

Antoine Nonclercq a,∗, Martine Foulon b, Denis Verheulpen b, c, Cathy De Cock b, Marga Buzatu b, c, Pierre Mathys d, Patrick Van Bogaert c

a Laboratory of Image, Signal and Telecommunication Devices (LIST), CP165/51, Université Libre de Bruxelles (ULB), Avenue F. Roosevelt 50, 1050 Brussels, Belgium
b Department of Pediatric Neurology, Centre Hospitalier Universitaire de Charleroi, Boulevard P. Janson 92, 6000 Charleroi, Belgium
c Department of Pediatric Neurology, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Bruxelles, Belgium
d Bio, Electro and Mechanical Systems (BEAMS), CP165/56, Université Libre de Bruxelles, Avenue F. Roosevelt 50, 1050 Bruxelles, Belgium

HIGHLIGHTS
- An automated cluster-based spike detection algorithm is proposed.
- It was tested in recordings with continuous spike and waves during slow wave sleep.
- It performs similarly to three EEG experts.
- It shows little difference with an expert in spike-and-wave percentage evaluation.
- The algorithm adapts to different types of recording in a fully automated way.

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ABSTRACT

Visual quantification of interictal epileptiform activity is time consuming and requires a high level of expert's vigilance. This is especially true for overnight recordings of patient suffering from epileptic encephalopathy with continuous spike and waves during slow-wave sleep (CSWS) as they can show tens of thousands of spikes. Automatic spike detection would be attractive for this condition, but available algorithms have methodological limitations related to variation in spike morphology both between patients and within a single recording.

We propose a fully automated method of interictal spike detection that adapts to interpatient and inpatient variation in spike morphology. The algorithm works in five steps. (1) Spikes are detected using parameters suitable for highly sensitive detection. (2) Detected spikes are separated into clusters. (3) The number of clusters is automatically adjusted. (4) Centroids are used as templates for more specific spike detections, therefore adapting to the types of spike morphology. (5) Detected spikes are summed. The algorithm was evaluated on EEG samples from 20 children suffering from epilepsy with CSWS. When compared to the manual scoring of 3 EEG experts (3 records), the algorithm demonstrated similar performance since sensitivity and selectivity were 0.3% higher and 0.4% lower, respectively. The algorithm showed little difference compared to the manual scoring of another expert for the spike-and-wave index evaluation in 17 additional records (the mean absolute difference was 3.8%). This algorithm is therefore efficient for the count of interictal spikes and determination of a spike-and-wave index.

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* Corresponding author at: Laboratory of Image, Signal and Telecommunication Devices (LIST), CP165/51, Université Libre de Bruxelles, Avenue F.D. Roosevelt 50, B1050 Bruxelles, Belgium. Tel.: +32 2 650 30 86; fax: +32 2 650 47 13.
E-mail address: anonclerc@ulb.ac.be (A. Nonclercq).

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1. Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (Fisher et al., 2005). Epilepsy has variable etiologies, and affect both children and adults, and has an active incidence of 4–8/1000. Most epileptic patients show on their scalp EEG abnormalities recognizable by trained neurologists and called “spikes” in reference to their spike-like morphology. The presence of spikes is a marker of epilepsy, being significantly associated with the occurrence of epileptic seizures. In most clinical situations, precise quantification is not mandatory. In some specific cases, however, quantification of spikes is clinically relevant since the amount of spikes is related to the importance of brain dysfunction. This situation is encountered in epileptic encephalopathy (EE) with continuous spike and waves during slow-wave sleep (CSWS). EE with CSWS is an age-related epilepsy that presents with neurocognitive regression and an EEG pattern characterized by strong activation of the epileptic activity during sleep, with spikes that tend to diffuse over the whole scalp, and typically occupy more than 85% of slow-wave-sleep time (Tassinari et al., 2000). Proper diagnosis of EE with CSWS is very important, since it requires specific treatment, including corticosteroids (Buzatu et al., 2009).

Even if EE with CSWS is rather rare, two reasons justify the use of a detection algorithm: the fact that manual counting of the spikes may be time-consuming on a recording that can show tens of thousands of spikes, and the fact that achieving an accurate manual count on a long-term recording requires a high level of expert’s vigilance, which makes it a hard task and exposes to the risk of a decreased diagnosis accuracy. Hence, we decided to develop an algorithm and to test it against the scoring of EEG experts in patient’s records showing EE with CSWS.

Many automated spike detection algorithms have been published (as shown in Frost (1985), Wilson and Emerson (2002) and Halford (2009) for review). Algorithms are typically based on methods such as template matching (Ji et al., 2011), mimetic analysis (Exarchos et al., 2006), power spectral analysis (Sugi et al., 2002; Adjouadi et al., 2004; Exarchos et al., 2006), wavelet analysis (Adeli et al., 2003; Indiradevi et al., 2008) and artificial neural networks (Guler and Ufeyli, 2005; Tzallas et al., 2006). Newer methods include independent component analysis (De Lucia et al., 2008) and dithering (Casson and Rodriguez-Villegas, 2011).

One of the major problems of automatic spike detection is that both spike morphology and background vary widely between patients (interpatient variation) (Wilson and Emerson, 2002) as well as within a single recording (intrapatient variation) (Wahlberg and Lantz, 2000). This is why spike detection algorithms usually give better performance when the EEG expert is asked to select samples of spikes in order to tailor the algorithm to the patient (Sankar and Natour, 1992; Aarabi et al., 2009). However, this approach is not always suitable, as (1) it is time-consuming for the expert, (2) some infrequent types of spike morphology can be discarded, and (3) it reduces analysis reproducibility since results rely on these specific spikes that are scored by the expert.

In order to overcome the interpatient variation in spike morphology, a previous study by our group presented an original algorithm that automatically adapts to each patient (Nonclercq et al., 2009). Overall averaging was performed on all detected spikes to obtain the ‘average spike’ of the recording, which was then used to tailor the algorithm to the patient. When there is only little variation in spike morphology in the recording, such an averaging is meaningful. However, spikes found in a recording may belong to a few distinct classes corresponding to different foci (Engel, 1993). Averaging is then meaningless if performed on distinct groups of spikes. In order to overcome such a problem, spike clustering becomes necessary (Wahlberg and Lantz, 2000).

Clustering is the assignment of a set of spikes into subsets (called clusters) so that spikes in the same cluster show similar morphologies. Clustering may be performed in the temporal domain (i.e. applied to spikes present over a period of time), spatial domain (i.e. applied to spikes present in different derivations), or both.

Spike clustering has been widely used for the reconstruction of sources that generate the epileptiform discharges (Wahlberg and Lantz, 2000; Van’t Ent et al., 2003; Van Hese et al., 2008). It has also been performed to evaluate feature extraction and classification algorithms (Exarchos et al., 2006). It has been used in the temporal domain to separate spikes from other waves, using either raw data or parameterized data (Inan and Kuntalp, 2007). Similarly, it has been used in the spatial domain to reject events that were not located in an expected site (Aarabi et al., 2009).

Out of the many clustering algorithm used in EEG, k-mean is one of the best known (Inan and Kuntalp, 2007; Aarabi et al., 2009). It decomposes the spikes into a set of disjoint clusters, each cluster being defined by a cluster center, called centroid. The algorithm is iterative and works in two steps. First, each spike is assigned to the nearest centroid. Second, the position of each centroid is recalculated as being the mean of all spikes belonging to the corresponding cluster. The algorithm performs those two steps continuously until the assignment of spikes among centroids no longer changes.

This paper presents an automated detection algorithm that relies on temporal k-mean clustering to tackle interpatient and intrapatient variation in spike morphology. It uses centroids as templates that are specific to the types of spikes belonging to the cluster, in order to analyze individual types of spike morphology from the recording.

To evaluate the ability of the algorithm to quantify interictal epileptiform activity, two studies were conducted. The first one compared performance of three experts who scored EEG samples from three patients. The objective was to compare human experts (inter-expert study) versus the algorithm in terms of sensitivity, selectivity and detection correlation coefficient. The second study compared performance of a single expert versus the algorithm on 17 EEG samples from 11 patients. The purpose was to put the methodology into practice in the case of spike-and-wave index (SWI) evaluation.

2. Materials and methods

Patients, EEG samples selection and instructions given to the experts are identical to our previous paper (Nonclercq et al., 2009).

2.1. Patients

A group of children showing the CSWS syndrome was retrospectively selected based on the following criteria: (1) cognitive, language and/or behavioral deterioration and (2) CSWS pattern on sleep EEG. For study 1, three children (two eight-year-old girls and one nine-year-old boy) were selected from the database of the University Hospital of Charleroi. For study 2, 11 children, seven boys and four girls (sex ratio: 1.75) aged 3–13 years, were selected from the database of the Erasme University Hospital. All patients underwent sleep scalp EEG using either 11 electrodes (FP1, FP2, C3, C4, T3, T4, O1, O2, CZ, A1, and A2) or 21 electrodes placed according to the 10–20 International System. The recordings were performed with a 200 Hz sampling frequency and 12bit resolution.

2.2. EEG samples selection

For study 1, an EEG expert (M.F.) selected 21 short samples (6 samples for patients A and B, and 9 for patient C), which included
each sleep stages and awake recording. Samples had durations ranging from 70–370 s (234±92 s), and had an overall number of spikes of about 2500. The total duration of the samples was 23 min for patient A, 29 min for patient B, and 30 min for patient C.

For study 2, larger samples of sleep stages I and II, ranging from 20 to 30 min (29 min ± 2 min 30 s), were selected by an EEG expert. For each of the 11 patients, one sample was selected from a long-term EEG recording performed at the acute phase of the disease, and thus containing a lot of spikes. In six patients, a second sample was selected from a long-term EEG recording performed after corticosteroid treatment, and thus containing much less spikes. Thus a total of 17 EEG samples were analyzed. The overall number of spikes was about 25,000.

2.3. Instructions given to the experts and the algorithm

In both studies, the extracts were blindly and independently examined by each expert and by the algorithm. For study 1, three EEG experts (M.F., C.D. and D.V.) were asked to score all the spikes that they could find in the 21 extracts. For each patient, a derivation was chosen by one of the experts (M.F.) as being the one where the spikes did appear most clearly and the polarity of this derivation as being the one where spikes showed a negative amplitude: P3-O1 for patient A, FP1-F3 for patient B, and FP1-F7 for patient C. Each expert was then asked to score all the spikes of this given derivation. To help them in that task, they could examine additional derivations (FP1-F7, F7-T3, T3-T5, T5-O1, FP1-F3, F3-C3, C3-P3, P3-O1, FP2-F4, FP3-C4, C4-P4, P4-O2, FP2-F8, F8-T4, T4-T6, T6-O2, T3-C3, C3-CZ, CZ-C4, C4-T4 for patients A and B, and the same derivations with additional T3-A1 and T4-A2 for patient C).

For study 2, a quantitative grading system was used to analyze sleep EEG data. It consisted of a SWI calculation, which represented the average number of epileptiform discharges observed in the extract. This SWI was expressed in percentage and obtained by dividing the number of seconds presenting one or more spikes by the length of the extract and then by multiplying the result by 100. This procedure has been previously validated (Aeby et al., 2005; Buzatu et al., 2009). One EEG expert (M.B.) was asked to evaluate the SWI for the 17 extracts, by scoring spikes in all the derivations of a longitudinal montage. When 11 electrodes were used, the derivations chosen were: FP1-T3, T3-O1, FP2-T4, T4-O2, FP1-C3, C3-O1, FP2-C4, C4-O2, FP1-CZ, CZ-O1, FP2-CZ and CZ-O2.

The instructions given to the algorithm were identical to the ones given to the experts. In study 1, the algorithm was programmed to detect spikes in the same derivations as the experts. In study 2, the algorithm was programmed to find spikes in all the derivations of a given montage. To do so, the spike detection procedure was applied on each derivation of the montage independently. As there was no information about the polarity of the spikes, the procedure was applied for both polarities of each derivation (i.e. twice). The SWI was then calculated.

2.4. Description of the algorithm

The same method was used for both studies. It works in five steps (Fig. 1).

2.4.1. First step: generic spike detection (Fig. 1a)

Data pre-processing (composed of first differential, squaring – keeping the sign – and smoothing) is applied to highlight the characteristics of the spike with respect to the background EEG. It is systematically applied to raw signal and template before any further processing.

A pre-selection is performed based on template matching that computes the cross-correlation between a given spike template and all signal frames (thus focusing on the morphology of the spike). Potential spikes must show a cross-correlation with the template greater than a threshold (called cross-correlation threshold) in order to be considered. The window length on which the calculations are made is chosen quite large (300 ms) to contain all possible spike morphologies (even the larger ones). A generic template is used. It is a stylized spike made of a triangle of 300 μV amplitude and 60 ms duration. This generic spike is in accordance with Chatrian spike definition (Chatrian et al., 1974).

Three features of the potential spikes (the rising and falling slopes as well as the curvature), chosen to distinguish a spike from the background, are extracted. Each feature of a potential spike must be greater than a fraction (called the features threshold) of the corresponding feature of the template to be considered as a spike.

Both the cross-correlation threshold and the features threshold are chosen quite low (respectively 60% and 30%) so that the detection is made highly sensitive to gather as many types spike morphology included in the recording as possible, at the cost of also including some artifacts.

2.4.2. Second step: temporal clustering (Fig. 1b)

The detected spikes are then characterized and sorted into clusters. Spikes are characterized by their pre-processed time series (i.e. the input of the clustering algorithm is made of the time series of each detected spikes that underwent the pre-processing defined in the previous section). This approach has been preferred over a parameterized approach because it has the potential advantage of avoiding possible false classification arising from data omission in EEG parameterization (Acir et al., 2005). Then, spikes are separated into clusters using k-mean algorithm.

2.4.3. Third step: cluster selection (Fig. 1c)

The number of clusters is automatically determined: starting from one single cluster, the number of clusters increases until one or more clusters contain less than 5% of the spikes, as previously proposed (van ‘t Ent et al., 2003; Liston et al., 2006). The cluster, or the clusters, showing less than 5% of spikes are discarded.

The proposed method has the benefit that the exact number of cluster needed to model the different spike morphologies within a recording does not need to be known. It is important because
finding this number is not trivial. This choice is usually tried out manually (Inan and Kuntalp, 2007). However, this task is time consuming and may reduce analysis reproducibility since results rely on the number of clusters chosen by the expert.

2.4.4. Fourth step: adapted spike detection (Fig. 1d)

A set of spike detections is performed. The detection procedure is identical to the one of the first step, but the templates and thresholds differ. Centroids are used as templates that are specific to the types of spikes belonging to the cluster. Detection is performed for each of those templates in order to analyze individual types of spike morphology from the recording. The detections are now made more specific to focus only on spikes that are similar to the centroids. To do so, the cross-correlation threshold and the features threshold are both increased (respectively to 80% and 50%). By this way, not only the algorithm adapts to the spikes of a recording, but the different types of spikes within a single recording are considered separately. Those templates are made on a statistical basis, so it would make no sense to generate them if the amount of the detected spikes was negligible. By this way, if the generic detection (first step) shows a SWI lower than 10%, the generic template is used here again instead of the centroids.

2.4.5. Fifth step: detection sum (Fig. 1e)

Finally, detected spikes are summed. As a single spike can be detected by various centroids, doubllets may appear. They are removed by the algorithm, so that each spike is only counted once.

By this way, the algorithm is automatically adjusted without the need of a priori knowledge from the experts. It is therefore fully automated.

2.5. Data analysis

2.5.1. Comparison of the algorithm with the experts

For study 1, sensitivity and selectivity were used to compare performance of the algorithm with the three experts who scored EEG samples. In order to do so, the average of all pairwise expert vs. expert sensitivity and selectivity values, and the average of all pairwise algorithm vs. expert sensitivity and selectivity values were compared, as proposed by Wilson and Emerson (2002). The sensitivity of one reader (A) versus another (B) is defined as:

\[ \text{Sensitivity}_{AB} = \frac{\text{spike}_{AB}}{\text{spike}_B} \]

where spike_{AB} is the number of spikes detected by both readers A and B and spike_B is the number of spikes detected by the reader B only. If reader B is taken as a ‘gold standard’, it measures the extent to which reader A is capable of detecting spikes. The selectivity of one reader (A) versus another (B) is defined as:

\[ \text{Selectivity}_{AB} = \frac{\text{spike}_{AB}}{\text{spike}_A} \]

and therefore it equals Sensitivity_{BA}. If reader B is taken as a ‘gold standard’, it measures the extent to which reader A is capable of rejecting false detections of spikes.

Furthermore, the detection correlation coefficient (Wilson et al., 1996), defined as the arithmetic mean of sensitivity and selectivity, was used to give an overall estimation of the algorithm and the experts.

Sensitivity, selectivity and detection correlation coefficient time/event-weighted averages over the three patients were also calculated to evaluate the algorithm and experts globally. It has been preferred over arithmetic mean, time-weighted average and concatenation of all samples, as it can correct for non-ideal samples in terms of duration and numbers of events (Casson et al., 2009). Time/event-weighted average is defined as:

\[ \bar{X} = \frac{1}{\sum_{i=1}^{M} T_i / N_i} \sum_{i=1}^{M} \frac{T_i}{N_i} \cdot X_i \]  

(3)

where \( \bar{X} \) is the time/event-weighted average, \( M \) is the number of samples and \( T_i, N_i \) and \( X_i \) are respectively the sample duration, the number of scored events and the chosen indicator (sensitivity, selectivity or detection correlation coefficient) for the \( i \)th sample.

The SWI index was used for the study 2. It was evaluated by an expert and calculated by the algorithm.

2.5.2. Evaluation of the improvement through clustering

Clustering allows the algorithm to adapt to variations in spike morphology by proposing templates (i.e. centroids) that specifically detect spikes respectively corresponding to them. By this way, improvement through clustering is related to the tendency of each centroid to detect spikes specifically related to it, i.e. that are not also detected by many other centroids. In order to evaluate it, the distribution of the amount of centroids jointly detecting a spike during the adapted detection (fourth step) was assessed. The first indicator chosen to evaluate the benefit of clustering for a patient is the average proportion of centroids jointly detecting a spike.

A specific correspondence between a given centroid and the group of spikes it detects is only possible if the morphology of this centroid differs from the one of the other centroids. By this way, a second indicator chosen to evaluate the benefit of clustering for a patient is the similarity among clusters. It was estimated with the average and minimum of all pairwise correlation between centroids.

Those two indicators are linked as similar centroids tend to detect similar spikes. For instance, in the extreme case where all centroids are identical (i.e. there is 100% correlation between centroids), identical spikes would be detected by each centroid (i.e. all centroids are jointly detecting each spike) and the clustering method would not show any benefit.

The relevance of the choice of the cluster being discarded (third step) was assessed by analyzing the amount of artifacts in each cluster. The artifacts were defined as events that were not scored by at least two experts (out of three).
Table 1 gives, for each patient, the sensitivity, selectivity and detection correlation coefficient of the experts and the algorithm. Time/event-weighted average performance is also shown.

3. Results

3.1. Comparison of the algorithm with the experts

3.1.1. Study 1

On average for all patients, the algorithm presented performance that was very similar to experts in terms of sensitivity, selectivity and detection correlation coefficient (e.g. the detection correlation coefficient was identical), although a bit more sensitive (as shown in Table 1). Patient B was more difficult to score, and led to reduced performance both for the experts and the algorithm.

3.1.2. Study 2

Results on the larger dataset (Table 2) showed, at the group level, that the mean absolute SWI difference between the algorithm and the expert was low (3.8%). The SWI evaluation of the algorithm was therefore close to the one of the expert, although a bit lower (0.4% lower in average). Individual comparisons between the expert and the algorithm showed that, for recordings 8 and 15, SWI difference exceeded 10%. This could be due to the presence of unclear spikes (such as smaller spikes compared to its background) and/or spike-like artifacts.

3.2. Evaluation of the improvement through clustering

The improvement through clustering was evaluated for the study 1. Fig. 2 shows that the distribution of the amount of centroids jointly detecting a spike differed between patients. In average, a spike was detected by 89% of the centroids (4.5 centroids out of 5) for patient A, 77% of the centroids (3.8 centroids out of 5) for patient B and 95% of the centroids (5.7 centroids out of 6) for patient C. Also, 88% of the spikes were jointly detected by all centroids for patient C, 82% for patient A and only 47% for patient B. Therefore the groups of spikes corresponding to the different centroids were more distinct for patient B than for the two other patients. The degree of similarities between centroids also differed between patients. The average correlations between centroids for patients A–C were respectively 90%, 84% and 97%, and the lowest correlations were respectively 72%, 58% and 93%. Patient B therefore also presents centroids that more clearly differ. It was expected since centroids that clearly differ also tend to detect different types of spikes. By this way, the benefit of clustering was the highest for patient B. Clusters and centroids obtained for this patient are given in Fig. 3. Fig. 4 shows an EEG sample from this patient where different types of spike morphology are detected by centroids with corresponding morphology.

Fig. 5 shows the amount of artifacts included in each cluster for the three patients. It shows that, for patient B, the discarded cluster also corresponded to the cluster that included the most artifacts. Discarding this cluster seems meaningful to avoid spike detection based on a template that includes a large amount of artifacts (94.6%). For patients A and C, the amount of artifacts in the clusters was low (24.1% or less for patient A and 2.6% or less for patient C). Therefore, regardless of the choice of the discarded cluster, detections would not be based on artifacts. Furthermore, as centroids are similar, the choice of the cluster being discarded is not expected to have a significant influence on the detection. Indeed, spikes that would not be detected by the centroid corresponding to the discarded cluster would be detected by all the other ones.

3.3. Time taken for the analysis

In study 1, the experts reported that the time necessary to score the spikes was about 60 min ± 30 min/h of recording. In study 2, the additional expert reported that the time necessary for SWI evaluation was about 40 min/h of recording.

When implemented on Matlab® R2007b and ran on an Intel Core 2 Duo 2.66 GHz, the analysis took 4.6 min ± 1.5 min/h of recording for study 1 and 45.5 min ± 30.2 min/h of recording for study 2.

4. Discussion

We show here that our algorithm dedicated for the quantification of interictal spikes in children suspected of having EE with CSWS presents performance that is very similar to three different experts in terms of sensitivity and selectivity (study 1). Indeed, when tested in EEG samples of 3 patients with CSWS, the detection correlation coefficient was identical. The method was put into practice in the SWI evaluation in a larger population and compared with evaluation of a single expert (study 2), showing similar results (3.8% mean absolute SWI difference; SWI difference lower than 10% for 15 out of 17 samples).

The time saved using the algorithm is substantial as manual spike counting takes about one hour per hour of recording. The time needed for the algorithm to perform the detection seems
adequate for clinical and research use, and could be much enhanced using a compiled language instead of Matlab®.

In study 1, improvement through clustering was higher for one of the 3 patients (patient B), as spikes detected by each centroid were more distinct and centroids more clearly different. As a consequence of the clustering method, variation in spike morphology defines the clusters which, in turn, define the centroids. Therefore, variations in centroids morphology reflect variation in spike morphology. By this way, patient B is expected to show more variation in spike morphology than patients A and C. Since the performance of the algorithm was similar to experts for all patients, it also shows its ability to perform well independently of the importance of those artifacts.
variations. This is important, as a spike detection algorithm should be reliable for any type of recording.

In the same study, the number of clusters varied between six and seven, depending on the patient. This amount seems typical as, in a previous study on spike detection using clusters (Inan and Kuntalp, 2007), from 2 to 6 clusters were tried out manually. The algorithm proposed in this paper being fully automated, it avoids this difficult and tedious task.

In study 2, in considering a threshold of 85% for the SWI during sleep to make a diagnosis of EE with CSWS, 2 patients (records 7 and 8) would have been diagnosed as EE with CSWS by the expert but not by the algorithm and vice versa for another patient (record 15). This could have important consequences in patient’s management. However, it should be kept in mind that the diagnosis of EE with CSWS does not rely only on a percentage of spikes during slow-wave sleep: associated symptoms, i.e. cognitive regression, have to accompany EEG abnormalities. It seems likely that diffusion of the spike-waves over the scalp during sleep are as important as the SWI to induce cognitive deficits, and that a diagnosis of EE with CSWS may therefore be posed in some patients having less than 85% spike-waves during sleep (Van Bogaert et al., 2006).

The heterogeneity of dataset and ways to assess performance makes direct comparison between other published spike detection algorithms difficult. However, based on the latest review proposed by Halford (2009), some comparison can be made since most algorithms also publish their results in terms of sensitivity and selectivity (18 algorithms have published both). Sensitivity and selectivity of the proposed algorithm was compared to each of those and it shows a higher sensitivity in 72% (13/18) of the cases and a higher selectivity also in 72% (13/18) of the cases. In average, sensitivity is 8.5% higher and selectivity is 10.3% higher. Thus, the comparison is very encouraging.

In conclusion, we have described an algorithm that automatically adapts to differences in spike morphology between patients (interpatient spike variation) as well as within a single patient (intrapatient spike variation) – hence exhibiting improved performance metrics, without the need of a priori knowledge from the experts. The algorithm shows performance similar to experts and could be used quite rapidly in common medical practice. The positive comparison with other spikes detection algorithms suggests that the proposed algorithm could also be used in other frameworks than EE with CSWS.

References


