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Despiking SEEG signals reveals dynamics of gamma band preictal activity

Nawel Jmail ^a, Martine Gavaret^{b,c}, F Bartolomei ^{b,c}, Christian-G. Bénar^b

a. Sfax University, ENIS, MIRACL, Tunisia

b. Aix Marseille Univ, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France

c. APMH, Hôpital de la Timone, Neurophysiologie clinique, Marseille, France

Corresponding author:

Christian George Bénar,
INSERM UMR 1106,
Institut de Neurosciences des Systèmes,
Marseille, France-13005
Tel: +33 4 91 38 55 62. Fax: +33 4 91 78 99 14
E-mail address: christian.benar@univ-amu.fr

Abstract:

Interictal epileptiform discharges, or "interictal spikes", are the hallmark of epilepsy. Still, there is growing evidence that oscillatory activity - whether in the gamma band (30-120 Hz) or at higher frequencies is another important marker of hyperexcitable tissues. A major difficulty arises from the fact that interictal spikes and oscillations overlap in the frequency domain. This hampers the correct delineation of the cortex producing pathological oscillations by simple filtering. Here, we propose a nonlinear technique for fitting the spike waveform in order to remove it, resulting in a "despiked" signal. This strategy was first applied to simulated data inspired from real stereo-electroencephalographic (SEEG) signals, then to real data. We show that despiking leads to a better space-time-frequency analysis of the oscillatory part of the signal. Thus, in the real SEEG signals, the spatio-temporal maps show a buildup of gamma oscillations during the preictal period in the despiked signals, whereas in the original signals this activity is masked by spikes. Despiking is thus a promising venue for a better characterization of oscillatory activity in electrophysiology of epilepsy.

1. Introduction

Electrophysiological brain signals in epilepsy show a complex mixture of patterns at different frequencies, reflecting the pathological activation of multiple neuronal networks. Signals can be broadly divided into two states, the ictal state (corresponding to seizures) and the interictal state (between seizures). The question arises of the existence of a third state - a "preictal" phase - where activity could in some cases build up and lead to the seizure (Wendling et al. 2005; Schwartz et al. 2011). In the interictal state, the most classical marker of epilepsy is the interictal epileptiform discharge (IED), or "interictal spike", a sharp transient lasting less than 50 ms (Gotman and Gloor 1976). Another important pattern, particularly visible in focal cortical dysplasia, is that of gamma-band epileptic oscillations, in approximately the 35-120 Hz band¹ (Hirai et al. 1999). Recently, much interest has been directed towards high frequency oscillations, the "fast ripples", in the 250-500 Hz band, which have been shown to be a good marker of the epileptogenic zone (Urrestarazu et al. 2007; Jacobs et al. 2008; Crépon et al. 2010). In the ictal period, a pattern of high interest is the fast discharge, which corresponds to a flattening of the signal, i.e., an increase in the proportion of high frequencies in the signals (Bartolomei et al. 2008). This pattern is classically considered as defining the seizure onset zone. Recently, automatic indices have been proposed in order to define the epileptogenic zone, based on the fast discharge detection or the contrast between high and low frequencies (Wendling et al. 2003; Bartolomei et al. 2008; David et al. 2011). Therefore, the question arises of the relationships between the high frequencies activities as measured in the interictal or pre-ictal state and those observed at the seizure onset.

A major difficulty in this task arises from the fact that interictal/preictal spikes and high frequency oscillations overlap in the frequency domain. Indeed, the extraction of the "pure" oscillatory component, i.e. not contaminated from filter ringing arising from spikes is a difficult issue. In particular, band-pass filtering spikes - which are sharp events by definition - produce spurious oscillatory patterns corresponding to the impulse response of the filter (Béнар et al. 2010). In the time frequency domain, the oscillatory and spike parts can be

¹ Limits of the gamma band are not clearly defined. Typically, the low gamma ranges from around 35 Hz to around 80 Hz, the high gamma band from around 80 Hz to 120 Hz.

better discriminated, but there can still be overlaps in the time-frequency domain (Ayoubian et al. 2013). Dictionary-based filtering, such as matching pursuit or basis pursuit are in theory quite robust to the overlap, but require that the (theoretical) dictionary be well matched to the real signals (Jmail et al. 2011).

The objective of this study was to propose a signal processing strategy for removing the epileptic spikes from the intracerebral signals. We show that this leads to better characterization of the regions involved in actual high frequency oscillations, in particular in the preictal-to-ictal transition. We tested the method on simulated data for different level of jitter between spikes and oscillations, and on real stereo-electroencephalographic EEG (SEEG) recorded in one patient during presurgical evaluation of epilepsy. Firstly, we describe the simulated and real datasets, and the algorithm for separating spikes and oscillations. Secondly, we depict the results obtained for both simulated and real data in terms of reconstruction accuracy and network measures. Lastly, we present conclusions and future directions.

2. Materials and methods

All signal processing was performed with the Matlab software (Mathworks, Natick, MA), version 2015a.

2.1. Simulations

We constructed simulations that reproduce a preictal series of epileptiform discharges , inspired by real SEEG traces, with a sampling rate set to 512 Hz. In the real data (see 2.2), we observed oscillations at different frequencies in the preictal period. Within the gamma band, oscillatory bursts were observed around 55 Hz and around 85 Hz (Supp. Fig. 1). Simulated data consisted of four components, corresponding to spikes, oscillations, seizure and noise. 100 realizations were constructed, one realization is shown on Figure 1.

Spikes were simulated as a sum of two gamma functions, using the *gampdf(x,a,b)* function in Matlab. With time variable x in samples, we set (a, b) to (9.8, 3.9) in channel 1, (7.8, 2) in channel 2, (11.7, 3.9) in channel 3 and (11.7,2) in channel 4. Amplitudes were set to 10, with fluctuation ranging from 10% to 25% (uniform distribution), except for the first gamma

function which presented no fluctuation. Time of occurrence of spikes was every 0.8s, with jitter ranging between 40 and 0 ms, except for the first gamma function.

Oscillations were simulated as oscillatory pulses, using the *gausspuls(t,fc,bw)* function of matlab, with *t* time, *fc* frequency of oscillation set to 55 Hz in channel 3 and 85 Hz in channel 4 and *bw* fractional bandwidth was set to 0.15 (corresponding to 7 periods of oscillations in the segment corresponding to the full-width half maximum). Amplitude fluctuations were set to 25% and 15% in channel 3 and 4 respectively, maximum temporal jitter to 50 ms and 40 ms in channel 3 and 4 respectively. The seizure part was simulated as two sine waves at 55 Hz in channel 3 and 85 Hz in channel 4, with envelope set to a Tukey window (*tukeywin* function of Matlab).

Noise was obtained by smoothing random Gaussian noise (function *randn* of Matlab) with a moving average of 10 points. Noise was set to an amplitude of 2 during the spike period, and 1 during the seizure period. A smooth transition between the two periods was ensured thanks to a half Tukey window, in order to avoid filter ringing arising from abrupt transitions.

2.2. Real signals

We selected presurgical intracerebral signals (stereo-electroencephalography, SEEG) in one patient with drug-resistant focal epilepsy from the Clinical Neurophysiology Department of the Timone hospital in Marseille. This epilepsy was symptomatic of a focal cortical dysplasia localized in the right occipito-temporal junction. The placement of depth electrodes was based upon available non-invasive information providing hypotheses about the localization of the epileptogenic zone. This patient presented a focal cortical dysplasia in the right lateral occipito-temporal junction. The SEEG data was acquired on a Deltamed System, sampled at 256 Hz, with anti-aliasing low-pass analog filter set to 85Hz. This particular SEEG recording was selected for the current study because it presented clear preictal patterns with regular spiking and visible epileptic oscillations. SEEG was using eight multi-contact depth electrodes (diameter 0.8 mm, 10 to 15 contacts, each 2 mm long with an inter-contact distance of 1.5 mm), positioned in the right hemisphere, implanted according to Talairach's stereotaxic method (Talairach and Bancaud 1973). Patients signed informed consent, and the study was

approved by the Institutional Review board (IRB00003888) of INSERM (IORG0003254, FWA00005831).

2.3. Spike modeling

We first detected spikes as events with high amplitude (in absolute value). In order to emphasize the transient part of the spikes, signals were first filtered in the 5Hz-40Hz band. Amplitude thresholds (on the signed values) were found based on data quartiles for each channel:

$$thr_{high} = Q_{0.5} + d(Q_{0.75} - Q_{0.25}) \quad (1)$$

$$thr_{low} = Q_{0.5} - d(Q_{0.75} - Q_{0.25}) \quad (2)$$

With Qp value in the distribution of amplitudes corresponding to the p percentile, and d distance parameter to be tuned heuristically. Typically, we found a value of 3 to be useful in most cases. Detections were found as the local peaks in the signal passing the amplitude thresholds, with a minimum distance between consecutive peaks set to 10 ms (function 'findpeaks' of Matlab). Then, for each detection, a model consisting of a modified Gaussian function was fitted non-linearly to the data:

$$G(t, a, b, \gamma) = \begin{cases} -Ae^{-\frac{[(t-a)+\gamma]^2}{b}}, & t < a \\ Ae^{-\frac{[(t-a)/\gamma]^2}{b}}, & t \geq a \end{cases} \quad (3)$$

With A amplitude, t time, a shift parameter (corresponding to zero of time), b scale parameters (width of the model function), γ asymmetry parameter (1 corresponds to the original - symmetric - Gaussian function). In order to estimate the parameters (a , b , γ) corresponding to the best fit, we used the non-linear simplex method (*fminsearch* from Matlab). Parameter A was fitted linearly by a least square method, with all other parameters fixed. The whole procedure results in a model of the spike components of the signal.

2.4. Spatio-temporal analysis

Time-frequency analysis was performed based on a Morlet wavelet transform with oscillation parameter $\xi=5$ (Bénar et al. 2009). Data were then presented under the form of

spatio-temporal maps (#channels x #time points). In a first representation, data were filtered in the frequency band of the oscillations (David et al. 2011), using the EEGLAB matlab function "eegfilt" (Delorme et al. 2004). A Hilbert transform was applied in order to estimate the envelope of fluctuations, followed by a smoothing of 256 ms. In a second representation this transform was normalized by dividing the map obtained at a lower frequency band, as in (Bartolomei et al. 2008).

In order to compute connectivity graphs, we used the nonlinear correlation h^2 (van der Heyden et al. 1999; Wendling et al. 2000). Window size was set to 2 seconds, the maximum delay to 100 ms, with a heuristic threshold set to 0.35 on the original signals and 0.15 on the despiked signals.

The robustness of the procedure was validated on a series of 100 realizations, in the two channels with a mixture of oscillations and spikes (channels 3 and 4). For each realization, we computed the correlation coefficient between the simulated data filtered in the band [35-95] Hz on the one hand and the simulated oscillations in the preictal phase on the other hand. This was done both on the original data and on the despiked data.

3. Results

3.1. Simulated data

We first tested the impact of the despiking procedure on the filtered data in the temporal domain, on one channel of simulated data (channel 4, presenting a mixture of spikes and oscillations at 85 Hz). Results are presented in Figure 2. On the original signals (Fig 2a), the (sharp) spikes produced filter ringing (i.e. spurious oscillations) that arise from the impulse response of the filter (Fig. 2b), of shorter duration but higher amplitude than the actual oscillation. Such oscillations are often referred to as 'Gibbs effect' - although originally the Gibbs phenomenon was obtained from Fourier Series - and have been called 'false ripples' (Bénar et al. 2010) in the context of epilepsy. This implies that energy will be detected in the gamma band whenever spikes are present, whether accompanied by actual oscillations or not. In contrast, for the despiked signal (Fig2c), the impact of the high-frequency part of the spike has been drastically reduced (Fig 2d). This implies that the filtering procedure will be much more specific for detecting actual oscillations, reducing the false detections produced

by filter ringing. In supplementary Figure 2, we illustrate this effect for simulated oscillations with higher frequency (in the fast ripple band), in both a channel with a mixture of spikes and oscillation and a channel with no true oscillation.

We computed the ratio between the amplitude of the despiked signal versus that of the original signal, at the peak of the first (i.e., sharper) wave. The median ratio across channel, events and realizations was 4.6% (quartiles 1.7% - 7.5%), which means that most of the time of reduction of the spike of more than 90% was obtained. We did the same computation for the envelope of signals filtered in the 35-95Hz band. In channel 1, the median ratio was 48.9% (quartiles 47.8% - 50%). In channel 2, with sharper spikes, the median ratio was 13.7 (quartiles 12.6 %- 15.3%).

As the distinction between spikes and oscillations is often better done in the time-frequency plane (van der Heyden et al. 1999; Wendling et al. 2000; Bénar et al. 2010; Jmail et al. 2011), we studied the impact of despiking signals on the time-frequency representation of signals. An example is shown in Figure 3, corresponding also to channel 4. On the original signals (Figure 3a), spikes result in a wide-band pattern, and one can easily picture that depending on the time lag between spike and oscillations, the spike part could cover the 'blob' corresponding to the oscillation (Jmail et al. 2011). On the despiked signals (Figure 3b), the oscillatory part is more visible on the time-frequency representation.

A useful representation in clinical practice is based on a spatio-temporal map, where signals are filtered in a frequency band of interest (David et al 2011), with possible division by energy in low frequencies (Bartolomei et al 2008). This help mapping channels where the seizure starts, where typically there is a sudden increase in high frequency content and lowering of low frequencies (Bartolomei et al 2008). In Figure 4, we illustrate such representation on the simulated data, with or without despiking. On the original signal, when filtered in the frequency band that contains oscillations (35-95Hz), a high energy level is visible on all channels presenting spikes, whether presenting actual oscillations or not (Fig. 4a). After despiking, there is better discrimination of channels with actual oscillations (Fig. 4b) - only little residuals from filtered spikes remain. When normalizing by low frequencies, all channels present low values, even when there are actual oscillations. Indeed, spikes present energy at all frequencies, and the division by energy in low frequencies thus

prevents detecting high frequency activity (Fig. 4c). The best representations (in terms of specificity) are obtained for maps after despiking (Fig. 4b and 4d).

Finally, we were interested in quantifying the gain in accuracy of reconstructing the oscillatory part of the signal obtained by the despiking procedure. We computed the correlation of both original signal and the despiked signal with the actual simulated oscillatory component, across 100 realizations and for the channels with oscillations (channels 3 and 4). The median correlation coefficient was 0.70 for the original signal (quartiles 0.57-0.82) and 0.93 for the despiked signal (quartiles 0.92-0.94), showing an improvement which is both highly significant, and robust to different realizations of noise (Fig. 5).

3.2. Real data

Real data consisted of a section of intracerebral EEG data, in the period immediately preceding the epileptic seizure (i.e., the "preictal" period). In Figure 6, we show the spatio-temporal distribution of automatic detections. A large number of spikes were detected (range 0-82, median 34), mostly in the preictal phase and in most channels.

Figure 7 shows a time-frequency analysis in one channel presenting both spikes and oscillations, on a subset of the time window. One can observe that in the despiked signals there is almost no spike left; only oscillations with some slow waves (which do not impact time-frequency representation in the high frequency range) remain. In the time frequency representation of the despiked signal (Fig 7d), clear bursts of high frequency activity are now visible (indicated by white arrows), which were masked in the original representation (Fig 7c) due to the high frequency part of the spikes. To be noted, some real spikes can present larger slow waves than what we decided to include in our simulations (Figure 1 and 2). However, this has no impact in the frequency bands of interest (above 15 Hz).

Finally, we computed the spatio-temporal maps on all channels, filtered in the 65-85 Hz band after normalization by the 8-30 Hz band (Figure 8). Interestingly, a buildup of gamma oscillations can be observed during the preictal period only in the despiked signals (Fig. 8b), whereas in the original signals this activity is masked by the high energy of the low frequency part of the spikes. Interestingly, several channels present energy in high frequency band

during the seizure onset, but no preictal oscillations, which suggest that seizure onset and interictal oscillations may be different biomarkers of the epileptogenic zone.

4. Discussion

Much attention has been dedicated so far towards characterizing the initial part of the seizure, the so-called 'fast discharge' in SEEG. this activity is visible on the traces as a flattening with high frequency content (Wendling et al. 2000; Worrell et al. 2008). Bartolomei and colleagues have used a normalized estimate of energy, dividing the energy in the high frequencies (12-97Hz) by that of low frequencies (3.5-12 Hz), which permits to emphasize the fast discharge (Bartolomei et al. 2008). David and colleagues (David et al. 2011) proposed to filter the traces in the gamma band only (60-100Hz), based on the work of Worrell and colleagues (Worrell et al. 2008), and to map the energy content in 3D. Gnatkovsky and colleagues (Gnatkovsky et al. 2011) have presented a similar approach, using a higher frequency band (110-125 Hz).

When applied to the interictal state, where gamma band activity has been shown to be clinically relevant (Palmini et al. 2004), these two approaches (simple filtering or ratio of energies) present drawbacks due to the presence of spikes. Indeed, in the filtered preictal signal (when using the (David et al. 2011) approach), the sharp part of the spike appears as an energy increase in the gamma band, whether an actual oscillation is present or not (Béнар et al. 2010). This tends to overestimate the extent of regions presenting high frequency oscillatory activity. On the contrary, when normalizing by the low frequency content (as in (Bartolomei et al. 2008)), the low frequency part of the spike will tend to mask the oscillations, and underestimate the extent of oscillatory activity.

A solution for improving the estimation of high frequency oscillatory activity even in the presence of spikes is to separate the spiky and oscillatory parts of the signal (Jmail et al. 2011; Chaibi et al. 2013). Models that are too constrained may not model adequately the spike part (Jmail et al 2011). Here, we propose to fit in a nonlinear manner the spike patterns and to remove this model from the signals (Jmail et al 2015). We used a model consisting of a single wave, which has the advantage of being flexible enough to be applied to sharp artifacts or spikes that can consist of one, two or three waves. However, this may

not be optimal as there could be interference between consecutive waves modeled separately. More complex models could be designed, using Bayesian inference (which could incorporate constraints on the covariance between parameters), or adaptive methods based on dictionary learning (Hitziger et al. 2013). Another important factor, apart from correct modeling of the spike wave, is the detection of spikes. Many methods exist for automatic detection of spikes (review in (Harner 2009)), and it would be interesting to compare them in the context of spike removal.

We show in simulated data that this approach permits to retrieve the correct spatio-temporal dynamics of the gamma band activity. In the real SEEG data, this allowed revealing a build-up of gamma activity occurring just before the seizure. Removing the spikes also allows having a better time-frequency representation of the oscillatory activity, without being masked by the spike part (Amiri et al. 2015 ; Roehri et al. 2016). Finally, it helps to better define the involved networks, which could be used in the level of graph definition and quantification by graph measures (Ponten et al. 2007).

The removal of the transient parts of the signal could be useful for other frequency bands, in order to better characterize the spatio-temporal dynamics of brain networks (Liu et al. 2015). Brain oscillatory networks in 'classical' frequency bands (from 1 Hz up to 120 Hz) could also be contaminated by the band-pass filtering of transients, requiring an adequate pipeline for separation (Selesnick and Bayram 2009). High frequency oscillations (HFO, between 120 Hz and 500 Hz) in the ripple and fast ripples bands (Urrestarazu et al. 2006; Chaibi et al. 2014) as well as physiological oscillations (Bragin et al. 2010; Waterstraat et al. 2016) could also benefit from such separation technique (see Supp Fig 2 for a preliminary test in the HFO frequency band).

Despiking could potentially be useful for other fields of neuroscience, where mixtures of transients and oscillations are present in the time series. For example, local field potentials present a mixture of oscillatory activity and sharp action potentials, and despiking could improve the investigation of correlations between LFP frequency bands and neuronal spiking (Mazzoni et al. 2010). Other modalities could also benefit from despiking, in particular EEG and MEG, where this could lead to a better characterization of the brain networks involved

in oscillations (Lina et al. 2014), in the preictal state (Gavaret et al. 2004), but also in the interictal phase (Malinowska et al. 2013; Jmail et al.2016).

5. Conclusion

The correct mapping of the actual oscillatory activity, uncontaminated by spikes, seems a promising venue in delineating the hyperexcitable tissues on the preictal signals. Such despiking should allow mapping separately the dynamics of the spikes and those of gamma oscillations, and thus to compare their clinical values as biomarkers.

Figures (screen captures, source files are of better quality)

Figure 1: One realization of simulated data, reproducing a preictal spiking pattern in channels 1-4 (between $t=0s$ and $t=6s$) followed by an ictal-like discharge in channels 3 and 4 (the simulated seizure start is at $t=7s$, indicated by two vertical arrows). In channels 3 and 4, oscillations were added to each spike (oscillations in the first spikes are indicated by tilted arrow heads).

Figure 2: Illustration of the despiking procedure. a) Simulated data (in blue, corresponding to channel 4 of Fig. 1) along with modeled spikes (in red). Spikes detections are shown as red circles. The model is a set of modified (asymmetric) Gaussian functions. b) Same signal filtered in the 35-95Hz (gamma) band. Strong filter-related ringing at the time of spikes are visible (red arrow), which correspond to the impulse response of the filter. The ringing waveforms have higher amplitude than the actual oscillations present in the signal (green arrow). c) Despiked signal, obtained by subtracting the modeled spikes from the original signal. The slow components remain, along with actual oscillations d). Same signal filtered in the 35-95Hz band. The true oscillations (within spikes, as well as the ictal discharge) are now clearly extracted; only a small residual from filtered spikes remain.

Figure 3: Time frequency analysis of simulated data (same data than Fig. 2). a) Original signal. In the time frequency plane, spikes present energy at all frequencies, producing an horizontal line (arrow). b) Despiked signal. The actual oscillations, corresponding to "blobs" in the time frequency plane (white arrow), now stand out better within their own frequency band.

Figure 4: Spatio-temporal maps (channels x time) of energy for the simulated data. a) Original signals, filtered in the 35-95Hz band. In the preictal period (0-6s), there is high energy visible in channels 1-4, corresponding to both channels with a mixture of spikes and true oscillations (channels 3 and 4) and to channels with only spikes (channels 1-2). b) Despiked signals. Mostly channels with true oscillations (channels 3-4) remain visible. c) Original signal with normalization by low frequencies (8-30 Hz). As spikes have energy across all frequencies, all channels have low energy values. d) Despiked signal with normalization.

Figure 5: Boxplots of the correlation coefficients between filtered data and the (pure) simulated oscillations, across 100 realizations of the simulated signals. On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually. On the original signals (left boxplot), the spurious oscillations arising from filtered spikes (filter ringing) result in low correlation values. On the despiked signals (right boxplot), correlation values are high, showing that the actual oscillatory part of signals were recovered.

Figure 6: Results of automatic spike detection, performed in the preictal period and the seizure start, on the real SEEG signals. Seizure onset is marked by a vertical arrow. There is continuous spiking in the preictal period (from 0 to 14 s), in most channels.

Figure 7: Time-frequency analysis in one channel (L9-L10), on a subset of the time window (from 10 to 14s). a) Original signal. Five high-amplitude spikes can be seen. Preictal oscillations are visible in the slow part spikes, especially for 4th one. b) Time frequency plane. Spikes produce high amplitude pyramidal-like shapes which hampers the visibility of oscillations. c) Despiked signal. Oscillations are more clearly visible already on the time-domain signal. d) Time frequency representation of the despiked signals. Oscillations can now be seen as 'blobs' (arrows).

Figure 8: Spatio-temporal maps of real signals (channels x time), filtered in the 65-85 Hz band with normalization by the 8-30 Hz band and smoothing by a moving average of 500 ms. a) Original signals There is no clear pattern in the preictal period (between 0 and 14s). Seizure start can be seen in several regions (arrows), with maximum energy ratio in channels L7-L8 to L11-L12 (arrow with tail). b) Despiked signals. Thanks to the decrease in the energy resulting from filtering spikes, a clear 'build-up' of oscillatory activity that leads to the seizure are now seen in channels L8-L9 to L10-L11 (arrow with tail).

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