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Burst on Hurst algorithm for detecting activity patterns in networks of cortical neurons

G. Stillo, L. Bonzano, M. Chiappalone, A. Vato, F. Davide, and S. Martinoia

Abstract— Electrophysiological signals were recorded from primary cultures of dissociated rat cortical neurons coupled to Micro-Electrode Arrays (MEAs). The neuronal discharge patterns may change under varying physiological and pathological conditions. For this reason, we developed a new burst detection method able to identify bursts with peculiar features in different experimental conditions (i.e. spontaneous activity and under the effect of specific drugs). The main feature of our algorithm (i.e. Burst On Hurst), based on the auto-similarity or fractal property of the recorded signal, is the independence from the chosen spike detection method since it works directly on the raw data.

Keywords— Burst detection, cortical neuronal networks, Micro-Electrode Array (MEA), wavelets.

I. INTRODUCTION

DUE to its extreme complexity, nowadays the neural code (i.e., how neurons in the brain represent, store and process information) is still poorly understood. A way to approach the problem consists in the study of the behavior of reduced and simplified systems, such as *in-vitro* networks of neurons, where the properties of the nervous system can be qualitatively characterized and modulated [1].

Neuronal networks process information by generating action potentials (i.e. spikes) and propagating them through spatio-temporal patterns of electrical activity that change with the development of the network and are modulated by external chemical and electrical stimulations.

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L. Bonzano’s Ph.D. fellowship is sponsored by Telecom Italia S.P.A.

G. Stillo is with Telecom Italia Learning Services (TILS), 00148, Roma, Italy, (e-mail: ue002493@guest.telecomitalia.it).

L. Bonzano is with the Neuroengineering and Bio-nanoTechnologies (NBT) group at DIBE, University of Genova, 16154, Genova, (e-mail: laura.bonzano@dibe.unige.it).

M. Chiappalone is with the Neuroengineering and Bio-nanoTechnologies (NBT) group at DIBE, University of Genova, 16154, Genova, (e-mail: michela@dibe.unige.it).

A. Vato is with the Neuroengineering and Bio-nanoTechnologies (NBT) group at DIBE, University of Genova, 16154, Genova, (corresponding author phone +390103532761; fax +390103532133; e-mail: vato@dibe.unige.it).

F. Davide is with Telecom Italia Learning Services (TILS), 00148, Roma, Italy, (e-mail: fabrizio.davide@telecomitalia.it).

S. Martinoia is with the Neuroengineering and Bio-nanoTechnologies (NBT) group at DIBE, University of Genova, 16154, Genova, (e-mail: martinoia@dibe.unige.it).

Electrophysiological activity is characterized by single spikes, bursts and silent periods. Commonly the term burst is used to identify a period in which a spike train is characterized by a much higher firing rate than other periods in the same train [2]. Using this qualitative definition, the detection of a burst is neither easy nor unambiguous.

In this work, we present a new method to identify the neuronal network bursting activity; we developed an algorithm based on the self-similarity property of the recorded electrophysiological signals and on the observation of the fractal-likeness increase during the “bursting” active state.

To confirm the efficacy of this new algorithm, a comparison with the results obtained using a spike analysis-based approach is presented.

II. MATERIALS AND METHODS

A. Neuronal preparation and experimental set-up

Neuronal cultures were taken from cerebral cortices of embryonic rats at gestation day 18 (E18). The cerebral cortex was dissociated using Trypsin. Cells were plated on 60 channels Micro-Electrode Arrays (MultichannelSystems, Reutlingen, Germany), pre-coated with adhesion promoting molecules (Poly-D-Lysine and Laminin), at the final density of $6\text{-}8\cdot 10^4$ cells/device and maintained in Neurobasal medium (Gibco) supplemented with 2% B-27 and 1% Glutamax-I (both Gibco). Measurements were carried out in physiological medium (NaCl 150mM, $CaCl_2$ 1.3mM, $MgCl_2$ 0.7mM, KCl 2.8mM, Glucose 10mM, HEPES buffer 10mM).

The electrophysiological signals were recorded using a standard commercially available experimental set-up for extracellular measurements (MultichannelSystems). Each channel was sampled at a frequency of 10 kHz.

B. Data set

Extracellular neuronal recordings were obtained by dissociated cultures of cortical neurons coupled to MEAs.

The data set employed to test the presented algorithm consists of electrophysiological signals recorded in three different experimental conditions: spontaneous activity (control), activity under addition of 30μM BIC (bicuculline, an antagonist of the $GABA_A$ receptor), activity under the addition of 100μM DL-TBOA (d,l-threo-beta-benzyloxyaspartate, a neuronal and glial inhibitor of glutamate transport). Recordings lasting 5 minutes of each experimental phase were considered for this analysis.

The choice of these drugs is motivated by the fact that they produce very specific burst patterns, as shown by the spike trains represented in Fig. 1. Whereas the effect of BIC is widely explained and motivated in the literature [3, 4], less it is known about the effects of DL-TBOA, acting both on the neuronal and glial cells [5-7]. Interestingly, the neuronal network behavior under TBOA addition is characterized by very long bursts, often not appropriately recognized by classical burst detection methods [8].

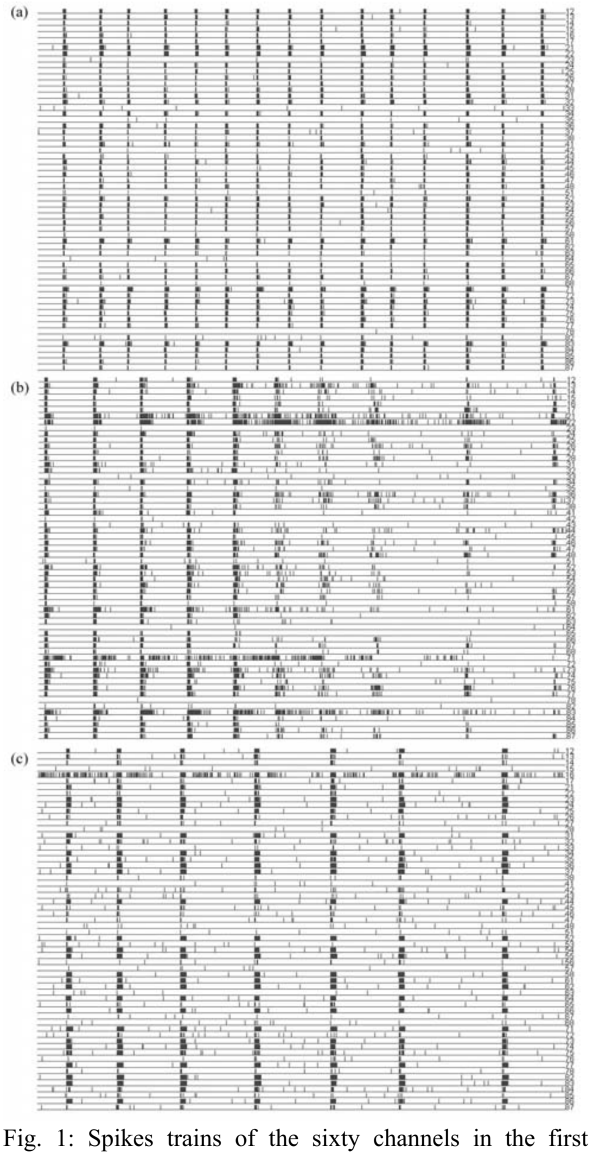

Fig. 1: Spikes trains of the sixty channels in the first 60 seconds of the experimental phases: control condition (a), TBOA addition (b), BIC addition (c).

C. Bust detection algorithms

As underlined in the introduction, bursting activity plays an important role during development and it is greatly influenced by chemical stimulation. A first step in the characterization of the network behavior is the capability to reliably detect and characterize such an activity.

To this end, several algorithms have been developed to extract burst features.

1) Classical Approaches

Many burst detection algorithms are based on the spike analysis and use a window to integrate the spike train signal and a threshold to detect the burst occurrence. In this paper the pseudo-integration algorithm (shortly BDPI algorithm) has been taken into consideration. A user-defined window shifts along the spike train at a step length, which is shorter than the window, generating a partial overlap between two successive windows. The spikes within each window are aggregated, generating the Activity Profile. Using a threshold it is possible to detect the presence of a burst obtaining the so-called Burst Occurrences Signal. It could be noted that the output sequence cardinality is lower than the input (spike train cardinality), i.e. the sequence has been “decimated”.

2) Wavelet-based approach.

Self-similarity is a common property of many natural phenomena, explained by the simple following relationship: given the temporal process $X_k = \tilde{X}(kT)$ (a continuous process $\tilde{X}(t)$ sampled at T), if the aggregated process

$$X_k^{(m)} = \sum_{j=(k-1)m+1}^{km} X_j \text{ with } k \in Z \tag{1}$$

satisfies the following property

$$m^{-H} X_k^{(m)} \cong X_k, m \to \infty \tag{2}$$

then the process X_k can be defined *self similar*, where *H* is the Hurst parameter containing the degree of auto-similarity of the process ($H \in [0,1]$, H=1 means completely auto-similar process). Observing that the fractal-likeness of the signal increases during the “bursting” active state, it is possible to characterize the bursting activity by evaluating a simple estimator E, based on wavelet decomposition, of the Hurst parameter H in a variable step window.

Fig. 2 shows an example of the application of the algorithm to an electrophysiological signal: it is important to remark that this method rejects automatically the noise through aggregation, being noise a random process, typically short range dependent.

The estimator is expressed by the following:

$$\hat{H} = \frac{1+M}{2} \tag{3}$$

where M is defined by [8]:

$$jM + C = \log_2\left(\frac{1}{n_j}\sum_k \left[d_x\left(j,k\right)\right]^2\right) \tag{4}$$

where $d_x\left(j,k\right)$ is the k-th coefficient of the detail of level j-th computed from the wavelet decomposition of the signal X.

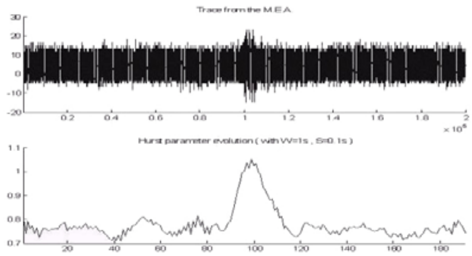

Fig. 2: An example of recorded signal and its corresponding Hurst parameter estimation.

This evaluation produces an estimate of H for each temporal window with length j. A burst is detected when the amplitude of estimator $\hat{H}$ is over an empirical threshold.

One of the advantages of this approach is that it is faster than the traditional one, consisting of filtering plus analysis of timing and amplitude of spike trains. Moreover a lower sensitivity to noise is documented (see Fig. 3).

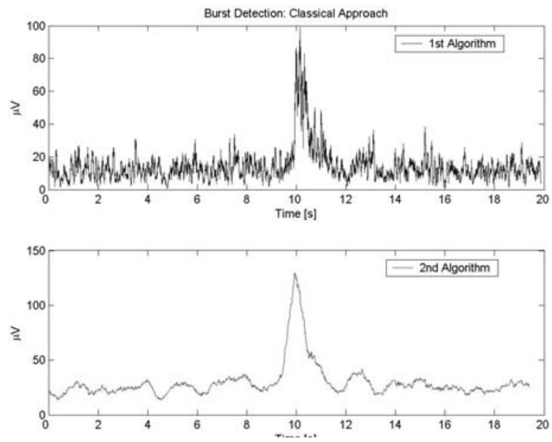

Fig. 3: Network activity estimated through the 1st traditional algorithm (based on the spikes timing and the amplitude) and the 2nd one (based on WMRA estimation of Hurst parameter). Burst occurs when the activity is over a threshold.

It is straightforward the implementation of (3) and (5) on a DSP based system, with the result of saving computing time with respect to other techniques.

III. Results and Discussion

A. Classical burst detection

To extract bursts using the classical algorithm we performed the following elaboration steps:

1. Extraction of firing events (spike detection)
   Spike detection was performed using an algorithm based on a Differential Threshold and on a refractory period.
2. Construction of the activity profile (pseudo integration of spikes)
   The spike train obtained from calculation (a) was aggregated for partially overlapping moving windows (the partial overlap reduced jitter).
   The calculation was based on the following parameters:
   - window: 500 ms
   - step: 50 ms
3. Application of a threshold to the activity profile and identification of bursts.

B. Burst on Hurst

The Burst on Hurst (BOH) algorithm uses a single pass to compute activity. The following parameters were set:

- Window: 500 ms (as in the previous example)
- Step: 50 ms (as in the previous example)
- Discrete Wavelet Decomposition level: 4
- Wavelet function: Haar
- interpolated octaves: from 2 to 4

The results of both algorithms were normalized to allow the comparison between them.

The duration of a burst was equal in both cases to the interval in which the Activity Profile was over the threshold value set at 1.33 (one third higher than the normalized maximum baseline activity).

C. Comparison

The results of the comparison between the two adopted algorithms are shown in Fig. 4, Fig. 5 and Fig. 6, in which raw data, activity profiles and detected bursts are shown for the three analysed recordings: control condition, TBOA addition and BIC addition respectively.

For recordings in control condition and TBOA addition, the results obtained with BOH were practically matching those with the classical approach. BOH also guarantees a high level of noise re-injection. As a process totally devoid of self-similarity, it has no effect on the estimation of the H coefficient [9]. At the same time, however, it fails to detect the burst events in the recording with BIC.

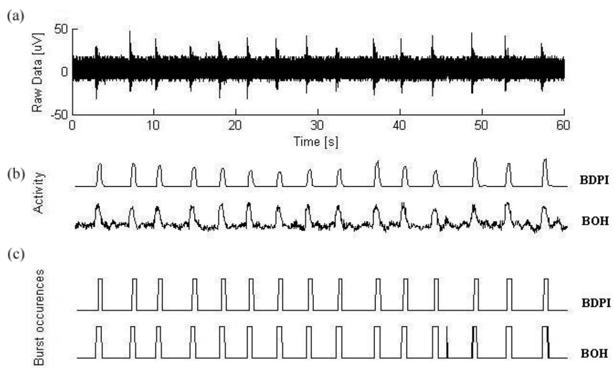

Fig. 4: Raw data (a), activity profile (b) and burst occurrences (c) elaborated using BDPI and BOH for 60 seconds of recordings in control condition (one selected channel).

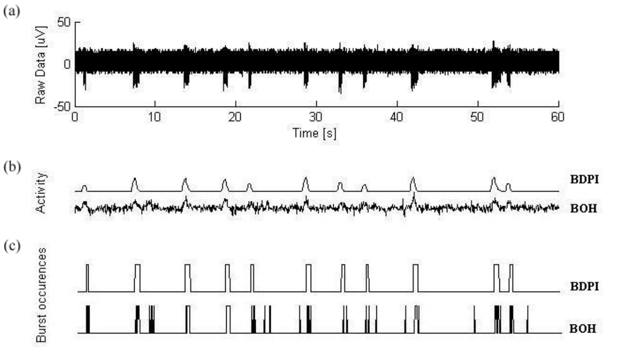

Fig. 5: Raw data (a), activity profile (b) and burst occurrences (c) elaborated using BDPI and BOH for 60 seconds of recordings with TBOA addition (one selected channel).

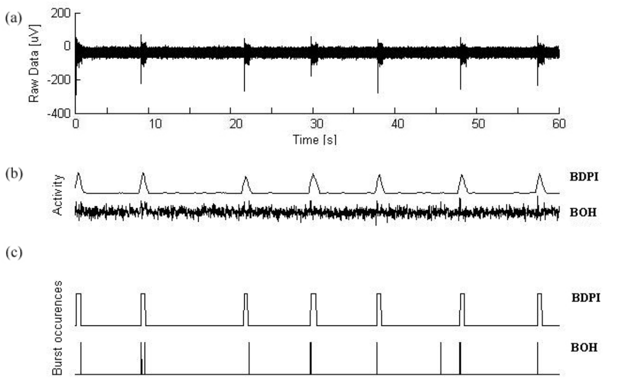

Fig. 6: Raw data (a), activity profile (b) and burst occurrences (c) elaborated using BDPI and BOH for 60 seconds of recordings with BIC addition (one selected channel).

The reason for this failure is that in recording with BIC addition, the GABA antagonist (bicuculline) significantly reduces the duration of burst events. Maybe the problem could be related to the acquisition frequency; in fact when these events are sampled at 10 KHz, they show no self-similarity at any scale. It seems reasonable to suppose that at a higher sampling frequency BOH would give good results even in these conditions and that a higher frequency would in general improve the overall algorithm performance.

TABLE I
NUMBER OF DETECTED BURSTS AND THEIR AVERAGE DURATION IN MS.

Recording [300 s]	Bursts Detected	Av. Duration [ms]
Control BDPI	73	482.88
Control BOH	74	441.1
TBOA BDPI	45	1037.2
TBOA BOH	46	888.15
BIC BDPI	27	475.76
BIC BOH	0	-

It could be noted that the length of burst events can be correctly estimated only if it is clearly comparable with shifting window length (in this case 500 ms). So the estimations obtained in recordings in control condition and with TBOA addition is not accurate using a 500ms window.

Thus it is important to remark how both algorithms (both applying the same step and windows) estimate the same durations.

IV. Conclusion

The advantage of this wavelet-based algorithm, with respect to classical spikes-analysis based algorithms, is the fact that it is directly applied on the recorded raw signals.

This is very important for extracellular recordings, because the spike detection can be source of ambiguity, since electrophysiological signals are embedded in a high level of noise.

The next step is to test the Burst On Hurst algorithm in different experimental conditions and verify the efficiency of the algorithm and the robustness when applied in the presence of different bursts shapes and frequencies.

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