

High-Order Correlations of Neuronal Spontaneous Activity Signals

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Abstract - A statistical characterization of spontaneous neuronal activity signals is presented. The first set of these signals results from *in vivo* measurements of action potentials of invertebrate neurons; the second set was recorded from cultured neurons based on a multielectrode-array (MEA) acquisition system. The correlations of second-, third- and fourth- statistical orders of these time series were estimated and compared to each other. Our experimental results provide the basis for considering the probability density function of spontaneous activity as nongaussian, and we also conclude that most of signals associated with MEA electrodes present a high-order correlated behavior.

I. INTRODUCTION

The research on neuronal coding involves several different approaches, such as point processes [1], random-walk models [2,3] and white-noise analysis [4]. All these approaches focus on interspike interval (ISI) time series, thus requiring the detection and sorting of spikes from the spontaneous activity signal (SAS) itself. Notice that such preprocessing is unavoidable, and it is subject to several errors due to the noise that frequently disturbs neurophysiologic instrumentation [5]. In addition, there are always uncertainties regarding the bound to be considered in order to establish whether a spike has taken place or not [3].

On the other hand, research on neuroprostheses [6,7] points out that longer could be achieved by means of decreasing the power required by the prosthesis operation. In consequence, it is necessary to reduce the computational complexity of algorithms, which suggests avoiding the task of sorting spikes. It would be also desirable to reduce hardware complexity, by replacing additive-noise filtering with a possible software solution.

High-order statistical signal processing [8] presents very interesting features for neural engineering purposes. For example, Gaussian noise effects, which often disturb

neurophysiologic measurements, may be overcome based on the following property. The high-order cumulants of a signal involving both SAS and Gaussian noise are exactly the same as the cumulants associated with just a SAS.

Moreover, high-order correlations provide further information on the probability density function, thus enabling more accurate signal classification and analysis under very low signal-to-noise ratio applications. In [8], the authors present different examples of several high-order classification algorithms, which present a very high performance for applications with signal-to-noise ratios under 5 dBs.

To our knowledge, few works of the literature discuss about the high-order statistical properties of the SAS. In [9], the authors present an analysis based on the 3rd-order correlations, applied to ISI time series. The gaussianity of SAS is also very few addressed.

Based on the previous motivations to apply high-order statistical analysis for neuronal coding, we have previously investigated in [10] the relationship between Hebbian plasticity and (non)linear prediction filtering. In [4,11,12], we have also discussed some issues on the white-noise properties of SAS.

In this paper, we further develop the high-order statistical analysis of SAS. Section II describes the acquisition of signals, whereas section III discusses the statistical tools and methods. Section IV presents the results and their discussion, which leads to the conclusions summarized in section V.

II. SIGNAL ACQUISITION

A. *In Vivo* Measurements of Invertebrate Neurons

Temporal sequences of intracellular spontaneous activity from identified neurons of the cerebral ganglia of the sea slug *Tritonia Diomedea* were obtained *in vivo* [13]. The animal was cut open, the conjunctive tissue extracted and the brain exposed. Without dissecting it, but maintaining the brain exposed to sea water, a glass electrode pulled for

intracellular recording was inserted into identified cells. Signals were recorded for at least 6 hours nonstop. Sampling time 0.1 millisecond/channel.

An example of the acquired spontaneous activity is presented in Figure 1. These signals will be labeled $i(n)$ throughout this paper, wherein the natural number “ n ” denotes the discrete time. Notice that $i(n)$ is not an ISI time series, but rather a SAS.

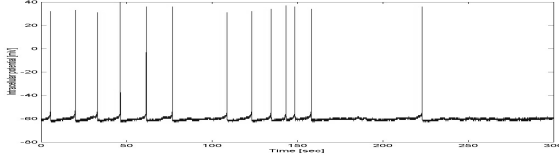


Fig. 1. Action potentials of the cerebral ganglia of the sea slug.

B. Multielectrode Array Signals

These signals will be labeled $m(n)$ throughout this paper. In our calculations, we have considered the SAS, measured from primary cultures of cortical neurons of embryonic chickens, cultured in Neuro Basal medium. SAS were measured by means of 60-planar microelectrodes arrays (MEA, Multichannel Systems), after 20 days in-vitro, in order to enable the maturation of synapses among the neurons. Sampling time is four milliseconds (4 ms). Further details are presented in [14].

III ESTIMATION OF HIGH-ORDER CORRELATIONS

A “pure high-order white noise of order p ” p , or $pw(n)$, is defined by the following equations [8,15]:

$$C_{mPW}(\tau_1, \tau_2, \dots, \tau_{m-1}) = R_{mPW} \delta(\tau_1, \tau_2, \dots, \tau_{m-1});$$

$$m \in \mathbf{N}^*; 2 < m < p \quad (1)$$

Where:

$C_{mPW}(\tau_1, \tau_2, \dots, \tau_{m-1})$: m -th order cumulant of $pw(n)$; $\tau_i \in \mathbf{N}$

$\mathbf{N}^*$: Set of nonzero natural numbers.

R_{mPW} : Real constant.

$\delta(\tau_1, \tau_2, \dots, \tau_{m-1})$: Generalized Kronecker symbol

$$\Delta$$

$$\delta(\tau_1, \tau_2, \dots, \tau_{m-1}) = \begin{cases} 1; & \text{if } \tau_1 = \tau_2 = \dots = \tau_{m-1} = 0 \\ 0; & \text{otherwise} \end{cases} \quad (2)$$

The 2nd-, 3rd- and 4th- order cumulants of a stochastic process $x(n)$ are respectively estimated as follows [8]:

$$\hat{C}_{2x}(\tau) = \frac{1}{K-1} \sum_{i=1}^{K-1} x(i).x(i+\tau); 0 \leq \tau \leq K-i \quad (3)$$

$$\hat{C}_{3x}(\tau_1, \tau_2) = \frac{1}{K-2} \sum_{i=1}^{K-2} x(i).x(i+\tau_1).x(i+\tau_2);$$

$$0 \leq \tau_1 \leq K-i; 0 \leq \tau_2 \leq K-i \quad (4)$$

$$\hat{C}_{4x}(\tau_1, \tau_2, \tau_3) = -3.(\hat{C}_{2x}(\tau_1, \tau_2))^2 +$$

$$\frac{1}{K-3} \sum_{i=1}^{K-3} x(i).x(i+\tau_1).x(i+\tau_2).x(i+\tau_3)$$

$$0 \leq \tau_1 \leq K-i; 0 \leq \tau_2 \leq K-i; 0 \leq \tau_3 \leq K-i \quad (5)$$

Where K is the length of the time series, or the total number of samples of $x(n)$ available for calculations.

The “whiteness indices” W_2, W_3, W_4 of a general stochastic process $x(n)$ are defined below, and discussed in detail in [8,11,12].

$$W_i = (W_p)^2; p = 2, 3, 4 \quad (6)$$

$$W_p = \frac{\left| C_{pX}(0,0,\dots) - \sum_{\tau_1=1}^q \sum_{\tau_2=1}^q \dots \sum_{\tau_{p-1}=1}^q C_{pX}(\tau_1, \tau_2, \dots, \tau_{p-1}) \right|}{\left| C_{pX}(0,0,\dots) \right|} \quad (7)$$

The values of q , used in (6)-(7), depend on the signal under consideration. Particularly, q must not be greater than the “stationary interval”, i.e., the period of time during which the signal keeps its statistical characteristics constant.

It should be noticed that, according to (1)-(2), W_p attains its maximum value in the case of the “pure high-order white noise”, for which $W_m = 1$ for any value of m within the interval $2 < m < p$. Notice also that, based on high-order theoretical results [8,15], if the stochastic process is periodic (e.g. bursting neurons), then W_m presents very low values, also including amplitudes close to zero.

Regarding gaussianity, a Gaussian stochastic process presents 3rd- and 4th- order cumulants close to zero, leading to whiteness indices W_2, W_3, W_4 of very high amplitude, which is always greater than 1 [8,15].

We considered five types of signals during our calculations. The first one is the invertebrate in vivo spontaneous activity $i(n)$ (see section II.A). The second one is the set of the 60-channel-MEA recordings $m(n)$ (see section II.B). The third one is a “high-order” white noise [8], which will be labeled here $hw(n)$. This signal is obtained by means of a special random number generator, which provides a time series with negligible correlations up to the

4th order. The fourth one is a cyclic clock signal, which is labeled as $c(n)$. This periodic time series is currently used for the synchronization of GPS systems, and it was generated by software according to a procedure defined in [16]. The fifth time series is labeled $g(n)$, and it was obtained by means of a standard random-number generator, so as to provide a Gaussian correlated stochastic process.

For each signal $\{i(n), m(n), hw(n), c(n), g(n)\}$, we carried out the following procedure. Firstly, we estimated the 2nd-, 3rd-, and 4th- order cumulants based respectively on equations (3), (4), and (5). Thus, the “whiteness indices” $W2$, $W3$, $W4$ were calculated based on (6)-(7). In this last case, we used τ as an integer multiple of sampling time. The quantity q in (7) was set to ten times the sampling time, which is equivalent to about forty milliseconds (40 ms) in the case of MEA data, or 1 ms in the case of invertebrate neurons. Since we have estimated the stationary time of these sets of signals as about 5.2 seconds, according to the results reported in [17], then the choices $q = \{1, 40\}$ ms are suitable values.

Table I presents the classification of signals based on previous theoretical results of the literature [8,15], as well as on our own experimental experience [10-12]. Notice that for whiteness indices that lie between 0.30 – 0.74, the time series is surely neither Gaussian nor periodic. In addition, it can not be classified as uncorrelated.

TABLE I
CLASSIFICATION OF SIGNALS BASED ON WHITENESS INDICES

Signals	W2, W3, W4
Pure high-order white noise (nongaussian)	0.75 – 1.00
Correlated (nongaussian)	0.30 – 0.74
Periodic (nongaussian)	0.01 – 0.05
Gaussian	$W3 > 23 - 25$ $W4 > 23 - 25$

IV RESULTS AND DISCUSSION

Tables II-V depict results which were obtained after averaging 100 Monte Carlo sequences of each signal. Each analyzed sequence had a length of 40,000 samples. In Table II, “ $pw(n)$ ” represents the theoretical definition of “pure high-order white noise”, as established by (1)-(2).

TABLE II
WHITENESS INDICES FOR INVERTEBRATE AND PURE WHITE-NOISE SIGNALS

Signals	W2	W3	W4
$i(n)$	0.85	0.85	0.82
$hw(n)$	0.90	0.90	0.85
$pw(n)$	1.00	1.00	1.00
$c(n)$	0.04	0.03	0.02
$g(n)$	25	24	23

In Table II, the whiteness indices associated with $hw(n)$, $c(n)$ and $g(n)$ defines, respectively, the practical bounds which characterize uncorrelated time series, periodic (bursting) activity and Gaussian stochastic processes. These

bounds are of paramount importance, since they will enable the classification of signals as white-noise, cyclic or (non)Gaussian. It should be noticed in Table II that the experimental whiteness indices for $hw(n)$, $c(n)$ and $g(n)$ agree with the results in Table I.

Table II points out that the invertebrate spontaneous activity is indeed an uncorrelated signal, since its whiteness indices are very close to the indices associated with the high-order white noise $hw(n)$.

Tables III, IV and V depict the classification of the signals recorded in several different MEA channels. It is interesting to notice that the results enable the classification of signals according to both Tables I and II. In addition, most of MEA signals are correlated. Four channels present a white-noise behavior (Table III) and just eighteen signals may be classified as bursting activity (Table V); whereas thirty-eight channels are classified as correlated (Table IV).

It should be pointed out that periodic signals take place in neighboring sites of the MEA.

TABLE III
WHITENESS INDICES FOR UNCORRELATED MEA SIGNALS

MEA Channel Number	W2	W3	W4
1,58	0.82	0.80	0.79
10,46	0.87	0.81	0.80

TABLE IV
WHITENESS INDICES FOR CORRELATED MEA SIGNALS

MEA Channel Number	W2	W3	W4
2,34	0.53	0.50	0.47
7,38	0.53	0.52	0.51
8,30	0.50	0.47	0.45
12,55	0.52	0.51	0.50
13,45	0.55	0.54	0.52
14,20	0.49	0.49	0.47
15,31	0.62	0.61	0.59
21,59	0.63	0.63	0.59
27,33	0.53	0.53	0.52
42,54	0.51	0.50	0.47
47,23	0.50	0.49	0.47
11,56	0.55	0.54	0.53
16,32	0.67	0.66	0.65
22,53	0.50	0.49	0.48
24,57	0.57	0.56	0.55
25,39	0.59	0.59	0.58
60,28	0.53	0.52	0.51
37,29	0.54	0.53	0.52
41,52	0.60	0.59	0.58

TABLE V
WHITENESS INDICES FOR BURSTING MEA SIGNALS

MEA Channel Number	W2	W3	W4
3,4,5,6	0.09	0.07	0.05
9,17,18,19	0.10	0.07	0.05
26,35	0.08	0.04	0.02
36,40	0.09	0.09	0.08
43,44,48,49	0.08	0.06	0.05
50,51	0.07	0.06	0.04

Finally, notice from all Tables II-V that the whiteness

indices present bounded values, or at least small values if compared to the indices associated with the Gaussian time series $g(n)$ (see Table II). In consequence, all spontaneous activity signals may be considered nongaussian stochastic processes.

V. CONCLUSIONS

This paper assesses the viability of the application of high-order statistical tools for neural engineering purposes.

We established experimental bounds on the 2nd, 3rd, 4th whiteness indices so that one can classify spontaneous activity signals as high-order white-noise (uncorrelated), high-order Gaussian, or high-order correlated. These bounds agree quite well with previous results presented in the literature [8,11,12,15]. Particularly, since spontaneous activity of invertebrate neurons is indeed a high-order white noise, current results confirm the conclusions of [4]. It was also outlined that MEA signals are mainly correlated, and there is a periodic bursting activity which takes place in neighboring electrodes. All spontaneous activity signals are nongaussian, which is the major condition for the application of high-order statistical signal processing techniques.

Future research requires calculation of correlations up to the 7th statistical order, in order to validate present results and those reported in [11,12]. Since all time series were supposed stationary, high-order correlations should be recalculated after segmentation of spontaneous activity signals.

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