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Bursting as a source for predictability in biological neural network activity

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Abstract

The role of bursting as a unit of neural information has received considerable support in the recent years. Experimental evidence shows that in many different neural systems, e.g. visual cortex or hippocampus, bursting is essential for coding and processing. We have recently demonstrated (Menendez de la Prida et al., 1996) the spontaneous presence of bursts in *in vitro* hippocampal slices from newborn animals, providing a good system to investigate bursting dynamics in physiological conditions. Here we analyze the interspike intervals (ISIs) of five intracellularly recorded cells from immature hippocampal networks. First, we test the time series against Poisson processes, typical of pure random behavior, using the Kolmogorov–Smirnov test. Only 2/5 records strongly deviate from Poisson process. Nonlinear prediction tests are then applied to compare original series with its Gaussian-scaled random phase surrogates and signs of short time predictability are observed (1/5). This predictability is originated by the intrinsic structure of bursts, in an otherwise purely random process, and can be removed completely by eliminating the bursts from the original time series. Here we introduce this method of eliminating bursts to get insight into the nonlinear dynamics of firing. Also the interburst intervals are indistinguishable from pure noise. The analysis of unstable periodicities within the bursts in the original ISIs shows that signs of nonlinearities can be statistically differentiated from their surrogate realizations (Pierson–Moss method). We discuss the computational implication of these results.

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1. Introduction

The search for determinism in neurophysiological time series has been a widely addressed question along last years [1]. The electrical activity from neuronal ensembles has been analyzed and signs of nonlinear

organization have been encountered [2]. However, these results are not categorical and in most of the cases only few records show clear evidences for determinism: 2/4 in [3], 1/6 in [4] and 4/7 in [5]. Since neuroelectrical data are by itself short, noisy and non-stationary high percentages of successful identifications are difficult to obtain with the available methods. Such a fact still keeps open the discussion of whether neuronal networks operate in a stochastic or a deterministic manner.

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Several investigations have mentioned the role of bursting in the nervous system [6]. Bursting is more efficient for synaptic transmission than single spikes, it participates in the neuronal coding for space and in some forms of short-term memory [7]. Although the mechanisms for generating bursts depend on the neuronal and network types, there are common aspects. Bursts come from the interaction of two dynamics: slow, representing the slow depolarizing wave, and fast, responsible for the spikes that crown it (see Fig. 1(A2) and [8]). Since the principal feature of neuronal coding is the adequate integration of presynaptic spiking, it does not matter by which mechanisms an event such as a burst is fired, but how the spikes are temporally arriving to the presynaptic contact in the integration period.

The hippocampal formation is specially prone to show bursting in several conditions [9]. We have recently shown that the spontaneous activity from hippocampal networks change from aperiodic bursting to a periodic spiking during the first postnatal month [10,11]. The reported findings of determinism in mature hippocampal tissue have been detected when analyzing data from induced bursting [4,12]. This is intriguing since as has been suggested, bursts seem to be the signal for computational purpose in biological neuronal network while in many cases single spikes are considered as noise [6]. The spontaneous presence of synchronized bursts in the newborn hippocampal tissue could be a source for its investigation in physiological conditions. This leads us to the main questions of the present work: *Is the bursting firing pattern generated from the immature neural networks indistinguishable from a random process? If so: Which part of the entire time series is responsible for such divergence?*

We addressed these two questions by applying tests from statistics and nonlinear analysis to the interspike and interbursts intervals (ISIs and IBIs, respectively) obtained from immature bursting activity. Like other groups we found tiny percentages of determinism in nonlinear prediction test (1/5). Since in our analysis, predictability disappears when eliminating the bursts in the original ISIs records and the IBIs are like random processes, we concluded that only the structure

within the bursts can result in positive predictability. We found unstable periodicities associated to the intrinsic dynamics of the bursts. Through the Pierson–Moss analysis [13] we found statistical differences when comparing the original and the surrogate time series (2/5).

2. Materials and methods

The experimental records were obtained from in vitro hippocampal slices as described previously [10,14].¹ The firing pattern from $n = 5$ pyramidal neurons were analyzed by computing the ISI from 5 to 10 min of stationary spontaneous activity (Fig. 1). ISIs have been extensively used to characterize experimental biological data [15]. In fact, Sauer [16] has recently shown that an eventually underlying determinism in an original time series can be detected by analyzing its ISI realization.

It has been previously shown that cells from extrastriate area MT fire Poisson-distributed bursts, which is typical of a pure random process [17]. Our analysis starts by testing ISIs against a Poisson process. For this purpose we compare the observed distribution function (ODF) with the theoretical distribution function (TDF). The ODF is obtained by ordering the ISIs concerning its size, i.e. by computing

$$\text{ODF}(x_e) = \frac{1}{N} \sum_{j=1}^N \Theta(x_e - x_j), \quad (1)$$

where $\Theta(z)$ is the step function (equal to 1 for every $z \geq 0$ and 0 otherwise) and x_e ranges from the minimum to the maximum values of the original ISI. For Poisson processes, the TDF satisfy the equation

$$\text{TDF}(x_e) = 1 - e^{-a \cdot x_e}, \quad (2)$$

where a is the inverse of the mean value of the original ISIs as derived from a maximum log-likelihood principle [18]. To quantify the differences in distribution

¹ Implementation of all the algorithms were performed in C and Matlab (V.4, Mathworks) in [14]. Graphic designs were performed with Origin (V.3.73, Microcal Software).

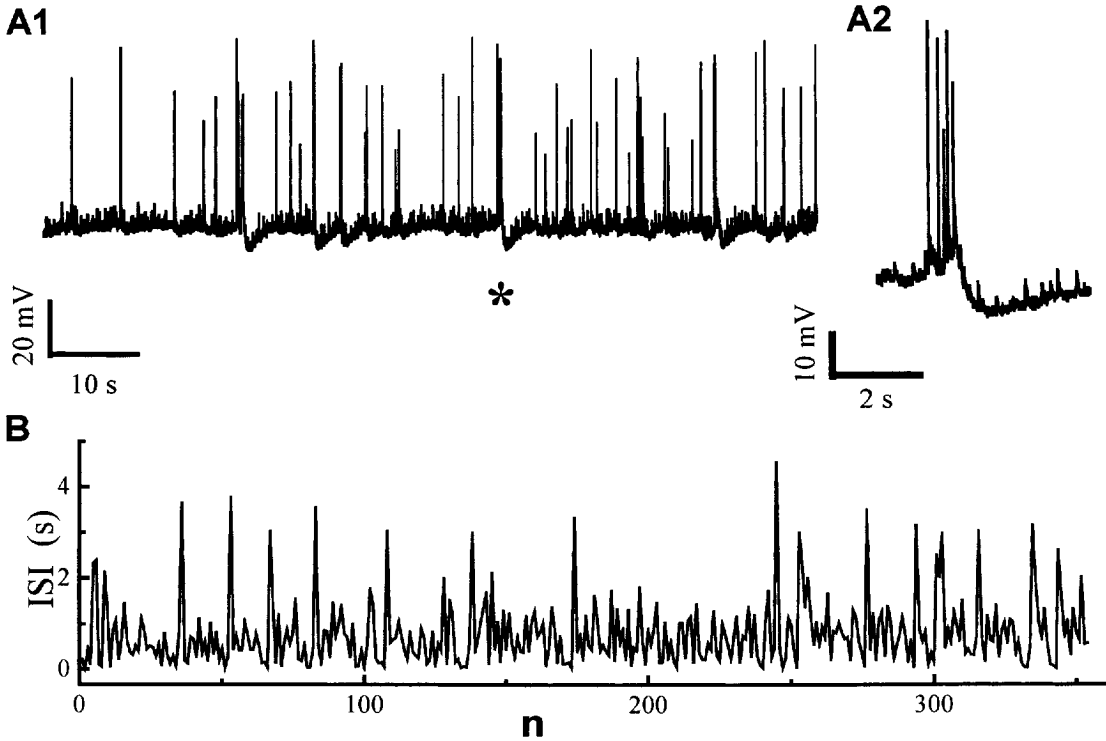


Fig. 1. Typical bursting firing pattern from biological neural networks and the interspike interval time series. (A1) Intracellular recording from a pyramidal cell of two postnatal day old subject (P2). The record was filtered at 1 KHz. (A2) A spontaneous burst, marked with an asterisk in (A1), is expanded. Bursts result from the interplay between a slow ionic current that constitute the depolarizing phase, and the fast spikes that crown it. (B) Interspike intervals (ISIs) from the original record.

between data and null hypothesis the Kolmogorov–Smirnov test (KS test) is used [19]. The KS test measures the maximal absolute distance between ODF and TDF,

$$\begin{aligned} \text{KS} &= \max_{x_e} |\text{ks}(x_e)| \\ &= \max_{x_e} |\text{ODF}(x_e) - \text{TDF}(x_e)|. \end{aligned} \quad (3)$$

The probability for KS under the null hypothesis to not exceed the observed value is

$$P(\text{KS}) = 2 \sum_{j=1}^{\infty} (-1)^{j-1} e^{-2j^2 \text{KS}(\sqrt{N} + 0.12 + 0.11/\sqrt{N})^2}. \quad (4)$$

Then $P(\text{KS})$ will assess on which percentage of the cases larger KS values occur in the null hypothesis than in the experimental data, allowing to decide

about the acceptance or rejection of a Poisson process. However, agreement in distribution with a pure random process is not sufficient to reject the hypothesis of determinism. Furthermore, from disagreement in certain parts of the distribution it is possible to obtain hints about where possible determinism might be located. A final answer can only be obtained applying a nonlinearity test, e.g. a test on short time predictability.

Determinism implies that an observable activity can be at least short time predictable, even if this activity looks like random. We use a nonlinear prediction test originally developed by Farmer and Sidorowich [20] and later applied to biological data [4]. We begin by selecting an E -dimensional embedding space which is defined as the set of points formed by

$$X_i = (\text{ISI}_i, \text{ISI}_{i+\tau}, \text{ISI}_{i+2\tau}, \dots, \text{ISI}_{i+(E-1)\tau}). \quad (5)$$

where τ is the time lag. The method consists in predicting the future of X_0 according to the tendency of its k neighboring points (X_i) when translated by the prediction horizon (H). The difference between the actual and predicted motion is the normalized prediction error:

$$\text{NPE} = \frac{\text{rms}\left(\left|X_{0+H} - \frac{1}{k} \sum_{i=1}^k X_{i+H}\right|\right)}{\text{rms}(|X_{0+H} - \langle X \rangle|)}, \quad (6)$$

where rms denotes root mean square and $\langle X \rangle$ is the mean [3]. Usually k is selected as 2% of the times series but we find better results by selecting 4% when working with our experimental data. In deterministic systems, NPE is small ($\text{NPE} < 1.0$) for small horizons, approaching 1.0 for increasing H . Random data have greater errors ($\text{NPE} \cong 1.0$) and do not show any particular region of H values in which lower NPEs occur.

To check statistically the result from original ISIs, we compare it with that obtained from the randomly shuffled variants, called surrogates [21]. The purpose is to create a new time series similar to the original in its linear statistics, but typically random. We used Gaussian-scaled random-phase surrogates to generate shuffled variants of every original ISI. If the results from both types of data are similar, then we cannot differentiate the original time series from the corresponding Gaussian-scaled surrogates. In this case, a deterministic organization of the original series should be rejected. Similar analysis has been previously applied to biological time series [4,5,22].

3. Results

The results from the KS test for the five ISI recordings are summarized in Table 1. We found that only the P1 and P7 time series strongly deviate from the Poisson processes. The values from these data sets mean that the null hypothesis of a Poisson process applies in less than $\varepsilon = 10^{-10} = 10^{-8}\%$. In Fig. 2(A) we represent the distribution functions from P7 ISI. As can be seen, there are more small ISIs in the ODF than expected from the null hypothesis (TDF). For larger ISIs the comparison is not as simple, since the

Table 1

Testing the experimental data against Poisson processes	
ISIs	Kolmogorov–Smirnov test KS; $P(\text{KS})$
P1	0.45; $> 1.0 - 10^{-10}$
P2	0.06; 0.78
P4	0.14; 0.99
P4b	0.14; 0.99
P7	0.50; $> 1.0 - 10^{-10}$

For every time series the values of KS and $P(\text{KS})$ are shown. Only P1 and P7 deviate from Poisson process. $P(\text{KS}) > 1 - \varepsilon$ with $\varepsilon = 10^{-10}$, indicates that the null hypothesis of a Poisson process applies in less than $\varepsilon = 10^{-10}$.

estimation of the parameter a is contaminated by the deviations in the smaller ISIs. We asked which part of the entire time series could be responsible for the deviation from a Poisson process.

We began by eliminating the bursts from the original time series, creating a treated one which only contains single spikes, no bursts. The burst detection procedure consists in defining the quantity δ , which represents the burst duration. The procedure eliminates the events that compose each burst by eliminating all the grouped ISIs lower than δ . The resulting data sets are called burst-corrected time series. KS test is then applied for each value of δ .²

Fig. 2(B) shows the results for P7 ISIs. As can be seen for small burst corrections of $\delta = 0.1$ s the probability is still higher than 0.98. However, for a wide range of δ ($0.11 \text{ s} < \delta < 0.50 \text{ s}$), the time series agrees well with a Poisson process, i.e. $P(\text{KS}) < 0.95$, obtaining a minimum at $\delta = 0.17$ s with $P(\text{KS}) = 0.57$ (see Fig. 2(B)). This is the range of burst duration in these cells, i.e. from 109 to 548 ms [10]. We show the effects of the burst correction for $\delta = 0.2$ s (Fig. 2(C)); the theoretical and the observed distribution match well in this case. The conclusion is that for this time series, deviation from pure random process only occurs if bursts are included. The remaining ISIs time series after burst elimination is composed by the time intervals between isolated spikes. Isolated spikes between the burst are thus the noise source in these time series [11].

² The method of eliminating bursts has been previously applied to physiological analysis [23] but up to our knowledge, it has not been applied to the nonlinear analysis of neuronal activity.

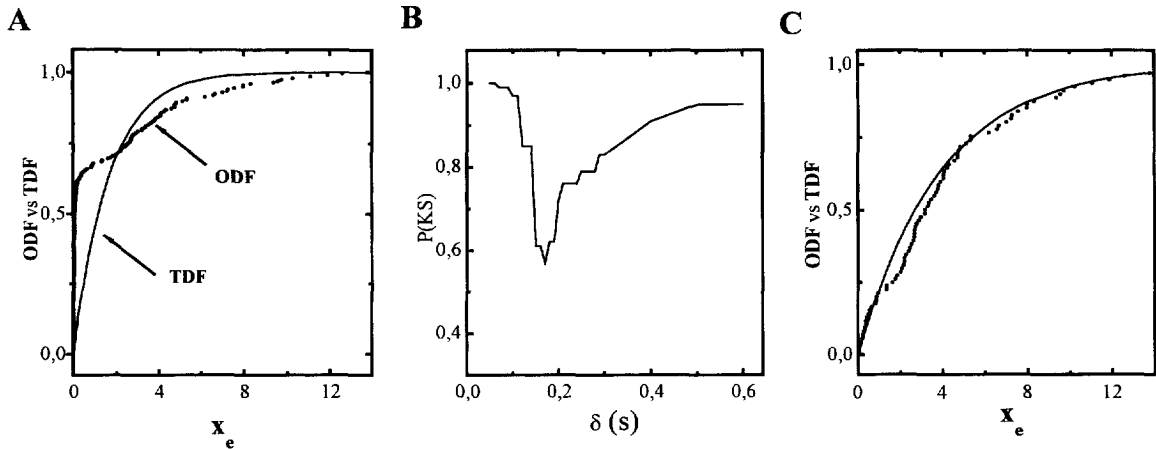


Fig. 2. Results from the distribution-test for Poisson processes. (A) Comparison of the observed distribution function, ODF, with the theoretical Poisson distribution function, TDF, for the original P7 time series, i.e. $\delta = 0$. Large deviation between ODF and TDF are visible especially for short time intervals. Here the parameter a in TDF (Eq. (1)) is equal to 0.61 s^{-1} . (B) Results from the distribution-test as a function of the correction for bursts. By means of δ , we eliminated the grouped events that constitute the bursts. The maximal accordance with a Poisson process is obtained in the range (0.11, 0.50) s which coincides with the burst duration range for P7 cell. (C) Comparison of the ODF and TDF from the burst-corrected P7 data set. Here $\delta = 0.2 \text{ s}$ and $a = 0.26 \text{ s}^{-1}$. As can be seen, the time series without bursts agrees well with a Poisson process.

Since information now only may be carried by the burst, the next step is to explore the IBIs. We constructed IBIs from P1 and P7 and applied KS test. For P1, $P(\text{KS} = 0.23) = 0.85$ and for P7 $P(\text{KS} = 0.19) = 0.61$. IBI time series are thus exactly Poisson from both, which agrees with previous findings [17]. All this suggests that the deviation from Poisson processes is occurring within the bursts. Whether this deviation results from the operation in a deterministic fashion or not could only be answered by applying prediction tests.

Nonlinear prediction from P1 failed for all the horizons, i.e. NPEs were above 1.0 for original ISI and mixed with NPEs from its surrogates. We rejected the deterministic hypothesis for this time series. NPEs from P7 are presented in Fig. 3(A). As can be seen, successful results from P7 ISIs are obtained up to embedding dimension 3, and up to horizon 6. Surrogates from these data show NPEs clearly separated from the originals. These results have the same tendency as those obtained if Henon equations were used for validation (data not shown, see [3]). We also tested the P7 burst-corrected series (Fig. 3(B)). No short time predictability is observed when compared with the

corresponding surrogates. All these findings were also confirmed through the computation of two other dynamical measures: second-order entropy and the product of inertia [10,24] that show clear differences from original and surrogate ISIs (unpublished results).

Our conclusion, based on these tests, is that predictability in P7 ISI time series could only be successful for low dimensions and for short horizons. Through KS tests applied to the original ISIs and IBIs and to the burst-corrected ISIs data we concluded that bursts may be the events responsible for the deviation from Poisson behavior in the original ISIs. By means of the nonlinearity test we can say that the divergence from Poisson process might be due to the nonlinearities. As previously cited, a number of theoretical studies have shown that neuronal bursts are built upon the interaction of two dynamics [8]. The bursts recorded in immature conditions are network driven events since their slow dynamics are produced by the synaptic action [25]. All this means that the way in which they are fired is an intrinsic property of the undeveloped hippocampal networks, and that, on the other hand, its activity is expected to be low dimensional. Our NPE results are in agreement with this last observation:

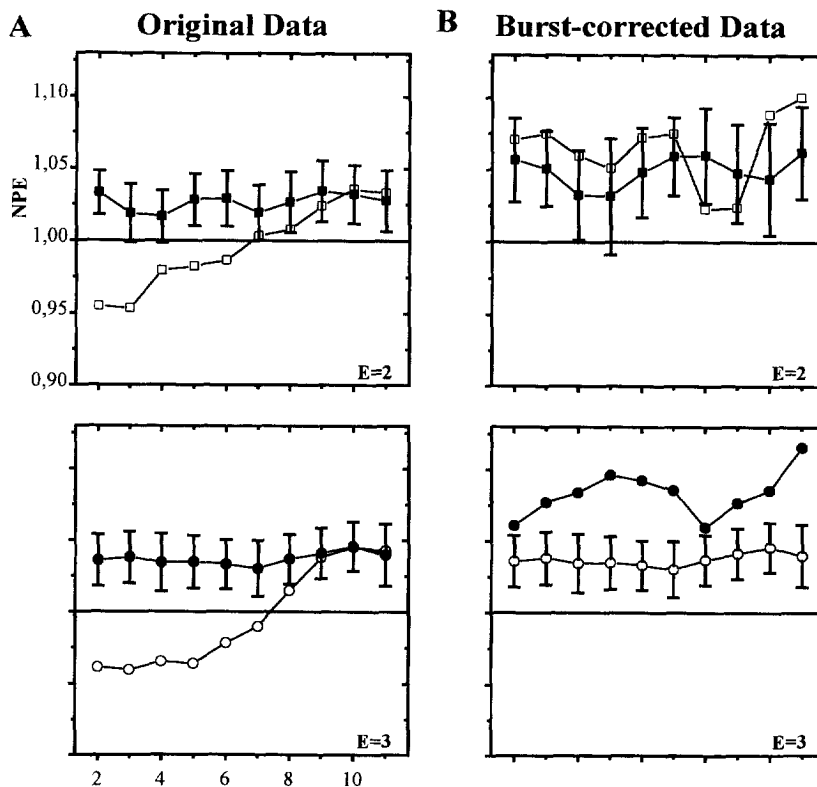


Fig. 3. Application of nonlinearity test to the experimental data. (A) Original experimental ISIs from P7 shows $NPE < 1.0$ for embedding dimensions 2–3 and for horizons up to 6. This indicates that the predictability hypothesis is successful for this experimental data set. An ensemble of 40 surrogates was computed. (B) The burst-corrected P7 time series, i.e. the original ISI without bursts, shows errors greater than 1.0 for every horizon and dimension. This corrected time series could not be differentiated from noise. Embedding dimensions (E) are indicated. In all the cases $H_{\max} = 11$ and $\tau = 1$ (see [34]) and $k = 8$. The x and y axes labels are the same as in the top and bottom left plots.

successful prediction in the original time series is obtained for low embedding dimension.

From a dynamical point of view, the bursts result from a periodic fast spiking that terminates when the membrane potential evolves towards the resting stable level (Fig. 1(A1)). This is called saddle–node bifurcation [26]. The saddles are a type of unstable periodicities, and a finger print of the chaotic dynamics. The instability leads the system to approach the periodic orbit at the depolarizing phase of the burst, as a result a group of spikes are fired, then the burst ends by reaching the resting potential (node). The approaching trajectory to the saddle shows another peculiarity: if we represent the timing of sequential spikes by plotting ISI_n versus ISI_{n+1} , the distance between suc-

cessive points and the saddle shrinks exponentially.³ The identification of determinism in experimental systems has used this property to analyze biological time series [28]. However, in a recent paper Christini and Collins [29] demonstrated that noisy systems can also mimic this saddle behavior. Pierson and Moss [13]

³ The outgoing trajectory also follows an exponential fashion. Nevertheless bursts may differ according to the structure of the spike patterns (see, e.g. Carpenter in [27]). In the case of these hippocampal bursts, that can be classified as Type I, the spiking frequency decreases, and the burst terminates abruptly at high frequency (homoclinic connection). Thus, the outgoing sequence is not present in our ISI time series. The burst is compounded by a group of ISI that shrinks exponentially and then a long ISI that indicates its end (see, e.g. Guckeheimer et al. in [27]).

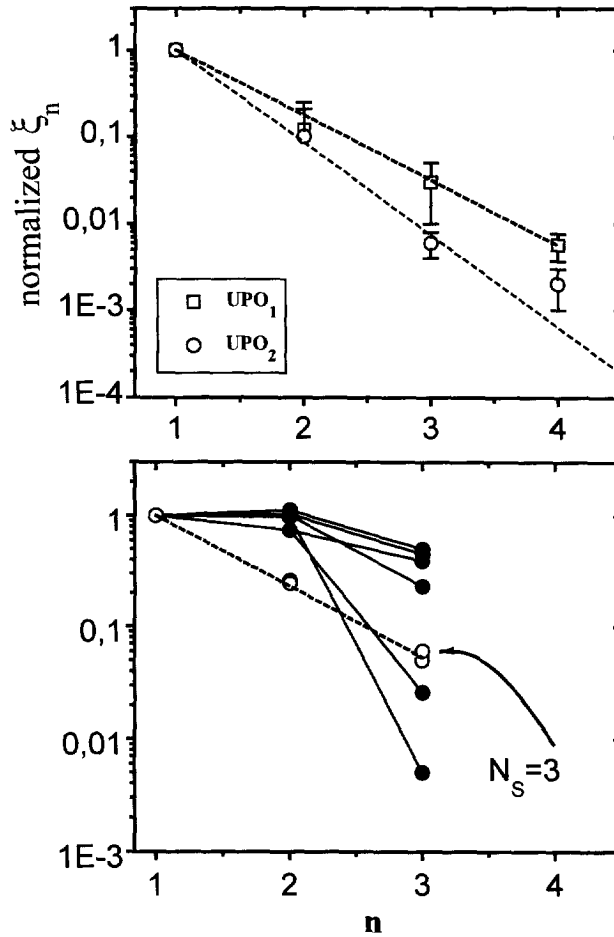


Fig. 4. Analysis of the approaching sequences to unstable periodic orbits (UPOs) within the bursts (see Fig. 1(A2)). The upper plot shows the exponential approaching sequences either to UPO_1 ($N = 6$) or UPO_2 ($N = 4$) (see text). On the contrary (bottom plot) in the surrogate data set only three show such a behavior when approaching UPO_1 (open circles) while 17 failed (closed circles, only six representative cases are shown).

solved this apparent problem showing that a reliable detection of chaos by this criterion is a matter of statistics.

The Pierson–Moss analysis consists in computing how many times candidates for unstable periodic orbits (UPOs) are encountered in the original time series and in its surrogates. If the original ISIs show larger numbers of positive occurrences than surrogates, then the determinism hypothesis applies well for it. We searched for the approaching sequence to the periodic spiking within each burst by computing the distance, in the (ISI_n, ISI_{n+1}) plot, between suc-

cessive points and the presumed saddle. We normalized this distance to the maximum, i.e. the distance of the first point in the approaching sequence, thus yielding the succession ξ_n for every approaching sequence. We found two possible UPOs, i.e. two ISIs from the periodic spiking in the burst: $UPO_1 = 0.032$ and $UPO_2 = 0.048 \pm 0.002$ ms. We counted how many of their approaching sequences follow an exponential scaling in original and Gaussian-scaled surrogate time series. The results are represented in Fig. 4. We found $N = 10$ exponential sequences in the 18 bursts from the original time series, against only $N_s = 3$ in the

surrogate (which contains 17 bursts) in the P7 time series. This confirms the prediction done previously [13], about the reliability of this method to detect determinism in noisy biological time series. We also examined the P1 time series which deviates from Poisson but failed to pass the prediction test. We have detected exponential sequences in four bursts from the original ISI against only two in the surrogates. The rest of the data does not show any statistical difference between original and surrogate ISI time series.

4. Discussion

We have applied a number of tests to analyze bursting in biological neural network activity. Using Kolmogorov–Smirnov test we have detected that two time series deviate from pure random processes being suitable for a deeper investigation. We found that the KS test is a very useful tool for the analysis of neurophysiological signals, especially because of its graphical advantage when analyzing short data sets, as previously suggested [11,19].

Further investigations using nonlinearity tests demonstrated that only one of these two records shows predictability (P7). Exponential approaches to unstable periodicities inside the burst were also examined. We have encountered 10 deterministic sequences in the original P7 time series while only three in its surrogates. Although examination of the P1 time series also show statistical difference when analyzing exponential approaching in the ISI time series, we had rejected previously the deterministic hypothesis for this record since it does not pass the prediction test. Based on all these analyses we conclude that signs of short-term predictability have been observed in one single record (1/5). This predictability, that can explain the deviation from Poisson processes, could only be detected in the timing of sequential events that compound the bursts.

The question is why if all the five time series contain bursts only one of them shows positive results for nonlinear structure. When looking at the experimental records it is clear that the level of spikes between bursts changes from cell to cell (see Fig. 1(A1)) and Fig. 1(A)

in [10]). Such a spiking behavior depends on the background synaptic noise [11]. The mean frequency of this spiking noise in the three cases that do not pass KS tests is 1.41 ± 0.04 Hz, against 0.5 Hz for P1 and 0.01 Hz for P7. No significant differences have been found in the burst frequency (2.8 ± 0.7 burst/min). We can account for the amount of spiking noise by computing the ratio between the length of the burst-corrected series against the length of the original one. The three negative cases show a mean of 0.84 against 0.55 for P1 and 0.43 for P7. This means that the single time series that successfully passes all the tests has the lower noise contamination.⁴ We suggest that the investigation of bursting dynamics from “cleaner”, i.e. bursting alone, intracellular neuronal activity will provide more successful results in nonlinear analysis.

Moreover, another more biologically related aspect should be mentioned. As previously stated, hippocampal immature bursts are network driven events [25]. The single positive result might support the existence of low-dimensional determinism derived from the activity of these undeveloped networks. Many works have shown low correlation dimensions when analyzing data from EEG in different physiological conditions [30], as well as from different in vitro preparations from older animals [4,12]. The low statistics of our results (1/5) does not sustain a wide generalization, but the fact that the brain shows spontaneously nonlinear organization from its very beginning might suggest that the elements needed to operate in a deterministic fashion are present at birth. Along development such neuronal elements could employ specific mechanisms to control the network activity while evolving towards adult conditions. The role of spontaneous activity in configuring such operative circuits have been recognized [31]. This is the case, for example, of the activity-dependent processes involved in the establishing of cortical columns [32]. These control strategies can play a relevant role in memory formation and information processing by the

⁴ There is another factor that could cause such a low statistic, i.e. the non-stationary of the original data and the surrogates. Surrogates are stochastic and linear but they could preserve some non-stationary frequency components that can affect the results.

neural circuits [33]. We suggest that the study of the immature neuronal activity can provide interesting hints to understand brain function.

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