Ongoing Hippocampal Neuronal Activity in Human: Is it Noise or Correlated Fractal Process?

Joydeep Bhattacharya[1], Jessica Edwards[2], Adam Mamelak[3], Erin M. Schuamn[2]

[1] Commission for Scientific Visualization, Austrian Academy of Sciences, Doanu City Str. 1/6, A1200, Vienna, Austria; e-mail: joydeep@oeaw.ac.at
[2] HHMI, Division of Biology, CalTech, Pasadena, CA 91125, USA
[3] Epilepsy & Brain Mapping Program, Huntington Hospital, Pasadena, CA, USA

Summary. The patterns of background or ongoing *in vivo* activity, even in the absence of any external stimulus, are quite irregular showing no clear structure or repetitiveness in the neuronal firing sequences. Consequently, the ongoing firing pattern of a neuron is mostly considered as a neuronal noise which is traditionally modeled as a stochastic Point process, i.e., renewal process which is devoid of any correlation between successive inter-spike-interval (ISI). But a recently emerging alternative view is that the ongoing activity may possess sptaio-temporally coherent patterns, a feature of fractal process with long-range correlation. Here, we investigated the nature of irregular fluctuations of ongoing neuronal firing pattern of neurons located in human hippocampus by the following methods: (i) detrended fluctuation analysis (DFA) , (ii) multiscale entropy (MSE) analysis, and (iii) convergence of the statistical moment analysis (CMA). Neuronal activity was recorded in the absence of any explicit cognitive task while the subjects were awake. Both the DFA and MSE analysis clearly show that the ongoing firing patterns are not well described by a renewal process, rather they show long-range power-law correlations, representing ongoing memory effects, which possibly arises from a fractal process. Further, these neurons showed slow convergence of statistical moments. Such long-range correlations are also corroborated by statistical control sequences. Neurons which exhibit long-range correlations also exhibit statistically non-significant correlations with other neighboring neurons. The presence of long-range correlations is a characteristic of fractal-like dynamics, representing memory or history in the firing patterns. We propose that this type of spatio-temporal correlations may be used to optimize information transfer and storage at hippocampal synapses. The presence of correlation in the ongoing pattern also suggests the influence of pre-stimulus sequence on shaping the post-stimulus responses. Further, these findings call for the modification of the existing neural modeling approaches.

1 Introduction

Spontaneous electrical activity, the neuronal activity which is observed in the absence of obvious external stimuli, is a prominent characteristic of the electrical activity of the central nervous system. Such ongoing or background activity is found from the microscopic level, recorded in the form of action potentials of a single neuron, to the macroscopic level, recorded in the form of global cortical oscillations. The principal feature of spontaneous activity is its extremely irregular fluctuations, i.e. lack of repetitiveness. The spontaneous activity is traditionally assumed as merely 'noise' in the nervous system which does not carry any meaningful information [1,2]. The obvious consequence of this assumption is that the post-stimulus response is uncorrelated to the pre-stimulus or ongoing responses. While analyzing single unit (i.e. neuron) data, the mean firing rate is proposed to possess the relevant stimulus-related information, while the temporal dependencies between successive action potentials (i.e. spikes) are completely ignored. In this framework, the inter-spike-interval (ISI) sequence of a single *in vivo* neuron is theoretically considered as a realization of a homogenous Poisson point process (HPP), i.e. renewal process (RP) [3]. The HPP is memoryless: the occurrence of a spike at any time t_1 is independent of the presence or absence of spikes at other times $t \neq t_1$. Hence, both the spike intervals and the spike counts form the sequences of independent, identically distributed random variables: there is no significant correlation present in the spike train generated by a HPP process, and the HPP interval process is completely described by the inter-spike-interval distribution function, which is a static measure.

Contrary to this assumption, recent findings [4-9] show that there are long-term correlations among ISIs. This long-range correlation is indicative of a fractal point process, which is statistically self-similar or scale-invariant. For a renewal process, higher-order interval and count distributions can be computed knowing only the first-order ISI distribution, but for fractal process, correlations and memory effects in the ISI sequence cannot be explained by the first-order ISI distribution. However, detection of the long-range correlation in ISI sequence with finite number of spikes is not a trivial task since it is shown [10-11] that certain signals may appear as a long-range correlated process according to one method but not necessarily according to another method. Thus, instead of emphasizing the results of one method, we recommend to perform multiple and complementary tests of correlation and compare the results to exclude the spurious findings of long-range correlation.

In this current study, we analyze the variability of spontaneous activity of *in vivo* single neuron recorded from human hippocampus. Our main aim is to investigate which process, renewal process or a fractal like process, better characterizes the fluctuations of the ISI patterns? A battery of methods was adopted. We observed that majority of the neurons showed long-range power-law correlations in their firing patterns and these neurons presented statistically significant inter-neuronal correlations. The presence of such long-range correlations is a strong signature of the fractal like process governing the neuronal dynamics.

2 Materials and Methods

2.1 Subjects & Data Recording

In this study, we analyzed the data recorded from a single subject (32 yr. male) who had pharmacologically intractable medial temporal lobe epilepsy. At the time of recording, the subject was in the hospital and had hybrid depth electrodes implanted for the precise localization of the epileptic focus. The surgery was performed by a neurosurgeon (A.M.); the electrode placement was solely guided by the clinical requirement. The complete clinical recording period lasted for 2 weeks and the research recordings were obtained using microwire bundles implanted within the depth electrodes. The microwire electrodes consisted of 8 identical Pt/Ir wires, which were insulated along the entire length, and protruded into the tissue approximately 5 mm beyond the tip of the depth electrode. The electrode locations were verified by post-implantation MRI. The research protocol was approved by the Institutional Review Boards; the patient provided written consent before the recording started.

Single unit data were sampled, at the rate of 32 kHz, and stored by the Cheetah^{TM} data acquisition system (Neuralynx Inc., Arizona, USA). In order to separate the ISI sequences of individual neuron, standard cluster cutting (using MClust version 2.0) computation was conducted. After carefully removing the ISI sequences which were noise-corrupted, 9 data sequences were selected for further processing. All recorded neurons were located in the left hippocampus. The subject was awake during the considered segment of recording and no external stimulus was presented to him.

2.2 Data Analysis

As stated earlier, the present study emphasized the importance of simultaneous usages of complimentary methods of fractal time series analysis. Briefly, the methods are sketched as follows.

2.2.1 Detrended Fluctuation Analysis (DFA)

This method was introduced by Peng et al. [12] and consisted of the following steps:

(a) For any ISI sequence $\{I(t),\ t=1,2,\ldots,\ N\}$, calculate the integrated sequence:

$$Y(k)=\sum_{t=1}^{k}I(t)-\langle I\rangle \qquad (1)$$

where $\langle I\rangle$ is the mean of the whole ISI sequence.

(b) Cut the sequence $Y(k)$ into $[N/n]$ nonoverlapping segments or boxes of size n. Since the record length N may not be a integer multiple of n, a short part at the end of the integrated sequence will remain. In order to take care of this remaining part, the same procedure of segmentation is repeated starting from the other end of the sequence. Thus, $2[N/n]$ boxes are produced.

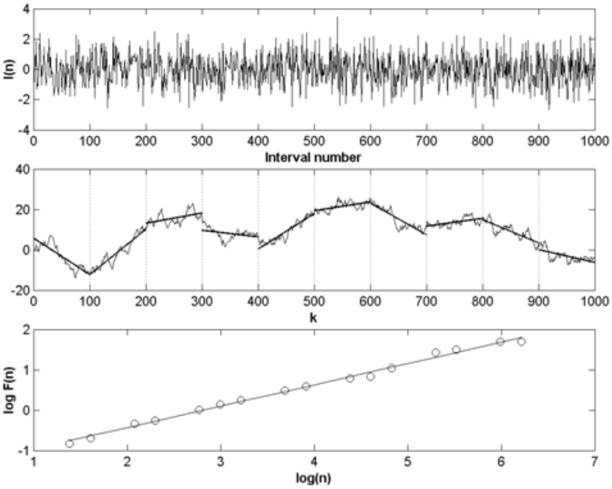

Figure 1: Illustration of the DFA method to investigate the scale-invariance and long-range correlations. *Upper*: Inter-spike-interval (ISI) time series, $I(n)$ of a hippocampal neuron. *Middle*: The solid profile indicates the integrated time series, $y(k)$, which is then divided into equal boxes of size n=100 spikes. The vertical lines show the boundaries between different boxes. The straight lines are the trends estimated in each box by a linear least-squares fit. It is to be noted that the ntegrated profile fluctuates around these trends. *Lower*: The root-mean-square deviations of these fluctuations, $F(n)$, are plotted against box size, n, on a log-log scale. If a straight line is found to be the best fit, the presence of power-law scaling is confirmed. The slope of the line provides the scaling exponent, α.

(c) Calculate the local trend within each box by a least-square fit. Then, detrend the sequence against the estimated linear fit. It is to be noted that higher order detrending can also be employed instead of linear one [13].
(d) For each of the $2[N/n]$ boxes, calculate the variance of the detrended sequence which was then averaged and the square root was taken to obtain the fluctuation function $F(n)$.
(e) Finally, calculate the fluctuation function for all possible box sizes (in this study, we vary n=3 to $N/3$].

For long-range power-law correlations in the ISI sequence, $F(n) \propto n^{\alpha}$. The scaling exponent, α, can be estimated by plotting $F(n)$ on a double-logarithmic scale. Fig. 1 shows the different steps involved in the computation of α.
For uncorrelated sequence and short-range correlations, $\alpha = 0.5$, while $0.5 < \alpha \leq 1$ indicates long-range correlations or power-law distributed values. Thus, α is an important measure to investigate the statistical correlation properties of a sequence.

2.2.2 Multi-Scale-Entropy (MSE) Analysis

A fractal process essentially represents a scale-invariant dynamics showing structures on multiple spatio-temporal scales. Because of that, the complexity (or entropy) of a long-range correlated ISI sequence should not depend on the resolution of the time scale of measurement. Here, we applied the measure of multi-scale-entropy (MSE) as introduced by Costa et al. [14]. First, the ISI sequence was coarse-grained by averaging a successively increasing number of data points in nonoverlapping windows. Each data point of the coarse-grained sequence, $I_{\tau}^{CG}(j)$, was calculated as follows: $I_{\tau}^{CG}(j) = \frac{1}{\tau} \sum_{t=(j-1)\tau+1}^{j\tau} I(t)$ where τ is the scale factor and $1 \leq j \leq N/\tau$. The sample entropy [15] of the coarse grained sequence was calculated. The profile of sample entropy against the scale factor is called the multi-scale-entropy, Z. Sample entropy reflects the conditional probability that the two pattern sequences of m consecutive data points which are in close resemblance to each other will also be similar when the pattern length increases by one point.

The multi-scale-entropy, Z, for uncorrelated or short-range correlated ISI sequence will monotonically decrease with τ, whereas Z will remain approximately constant for a long-range correlated or a fractal sequence.

2.2.3 Cumulative Moment Analysis

If a data sequence is long-range correlated, there does not exist any single average or mean value which can completely characterize the data. It indicates that as we collect more data points, the mean value continues to increase/decrease and the sample mean does not converge to population mean. But for nonfractal sequences, sample means exhibit quick convergence towards population mean. Here, we calculated the profile of cumulative mean for ISI sequence and qualitatively studied the convergent property. Although slow convergence of mean is not a definite proof of a fractal process, it provides complimentary, and often corroboratory, information to that obtained by the earlier methods.

2.2.4 Inter-neuronal Correlation Analysis

Earlier methods investigate history effects by analyzing the temporal correlation. However, it must be noted that history or memory in the firing pattern of a neuron needs

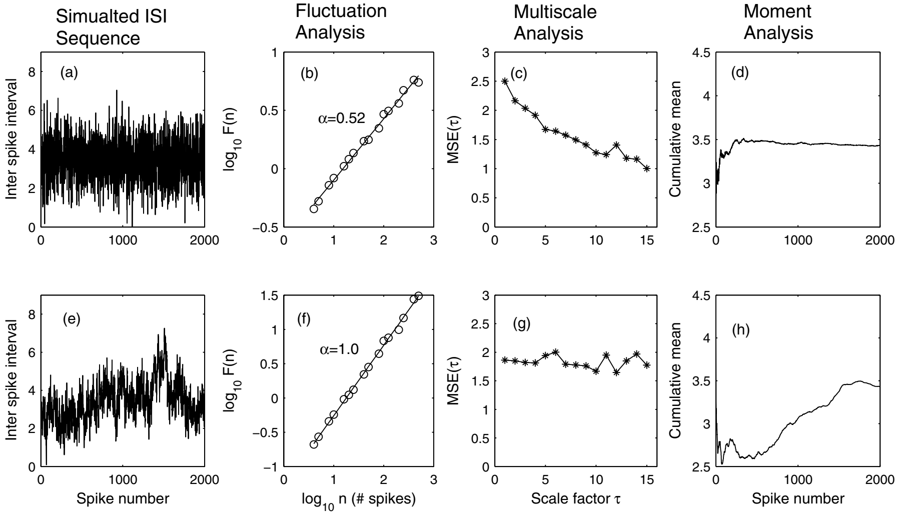

Figure 2: Applications of the battery of adopted methods to two simulated ISI sequences: (a) uncorrelated, random ISI, and (e) scale-invariant fractal ISI. The two sequences have identical mean, and amplitude histogram. The results based on DFA, MSE and CMA for the random ISI sequence are shown in (b)-(d) respectively. Similar for the fractal ISI are shown in (f)-(h).

to be stored somewhere but time is not a suitable substrate for the information storage. An immediate alternative medium of storage can be space, in the formation of a neuronal network. The possibilities of modification of the strengths of synapses and of the network architecture render the substrate medium to be dynamic. Our hypothesis was that those ISI sequences which were long-range correlated would present stronger coupling with one another than the other neurons showing renewal dynamics. The degree of inter-neuronal coupling was measured by calculating the correlation coefficient between two ISIs.

2.2.5 Statistical Control

Our null hypothesis was that the spike patterns were generated by HPP interval process. For this purpose, the original ISI sequences were randomly shuffled. Shuffling preserves the original mean, variance, and distribution information but destroys any correlation present in the original sequence. All of the earlier methods were also applied for a set of shuffled ISI sequences, which we termed as surrogate data set (we used 20 surrogates for each ISI sequence). To quantify the differences between the original and surrogate data set, the following score was computed: $Q = \left(R - \left\langle \{R_{shuff}\} \right\rangle\right) / std\left(\{R_{shuff}\}\right)$ where R is the value of any measure (e.g., α, Z) for the original sequence, $\{R_{shuff}\}$ is the set of values for same measure for the set of surrogates, and $\langle\cdot\rangle$ and *std* are the mean and standard deviation operator, respectively. If $Q > 1.96$, the null hypothesis of HPP or renewal process can be rejected with 95% statistical confidence.

3 Results

The battery of methods was first evaluated on simulated ISI sequences, random and fractal ISIs, and the results are shown in Fig. 2. Although these two sequences have same mean, variance and interval distribution function, their scaling and correlation properties differ from each other in a clear and convincing fashion. Further, mean of the randomly distributed ISI sequence quickly achieves a steady value (Fig. 2(d)), whereas mean of the fractal sequence does not show (Fig. 2(h)) any clear sign of convergence. Thus, these three methods offer confirmatory and conclusive evidences about the underlying correlated structure in the data sequence.

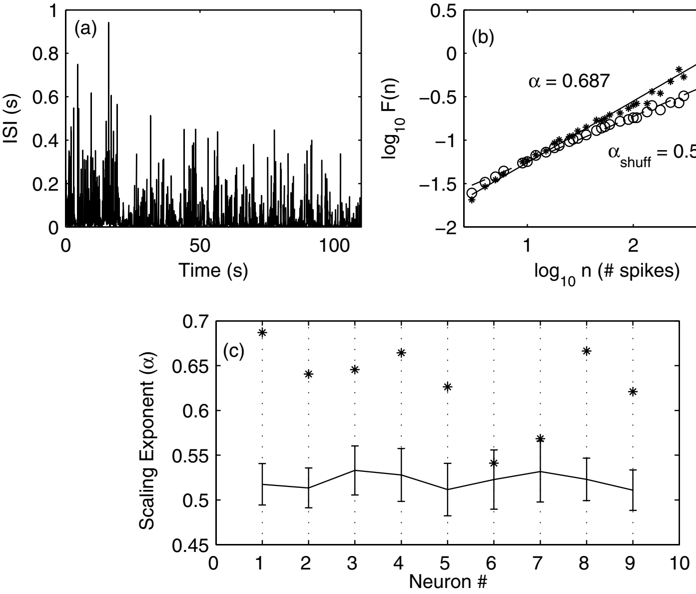

Figure 3: Detrended Fluctation Analysis. (a) ISI sequence of a single neuron. (b) Log-log plot of DFA method. The asterisks represent the original ISI sequence and the open circles are for the shuffled ISI sequence. (c) The scaling exponents for all nine neurons ('*'). The errorbars (mean±std) were calculated on the basis of 20 shuffled ISI sequences.

Next, we present the results of each analysis method of the true ISI sequences. Fig. 3(a) shows a segment of an ISI sequence of a typical neuron; a clear straight line fit was found in the log-log DFA plot (Fig. 3(b)) with $\alpha = 0.687$. When the ISI sequence was randomly shuffled, α is changed to 0.52 indicating the presence of long-range correlation in the original sequence. Fig. 3(c) summarizes the results of all 9 ISI sequences corresponding to 9 neurons. Seven ISI sequences showed significantly higher ($Q > 3$) α than their surrogate counterpart. Only one ISI sequence (neuron #6) could not be distinguished from its surrogates, and the remaining other neuron (#7) was found to be marginally significant.

Fig. 4 shows the MSE analysis. Like fractal process, many ISI sequences (Neurons #1,2,4,5,8) presented steady state entropy values at higher scale factor, while

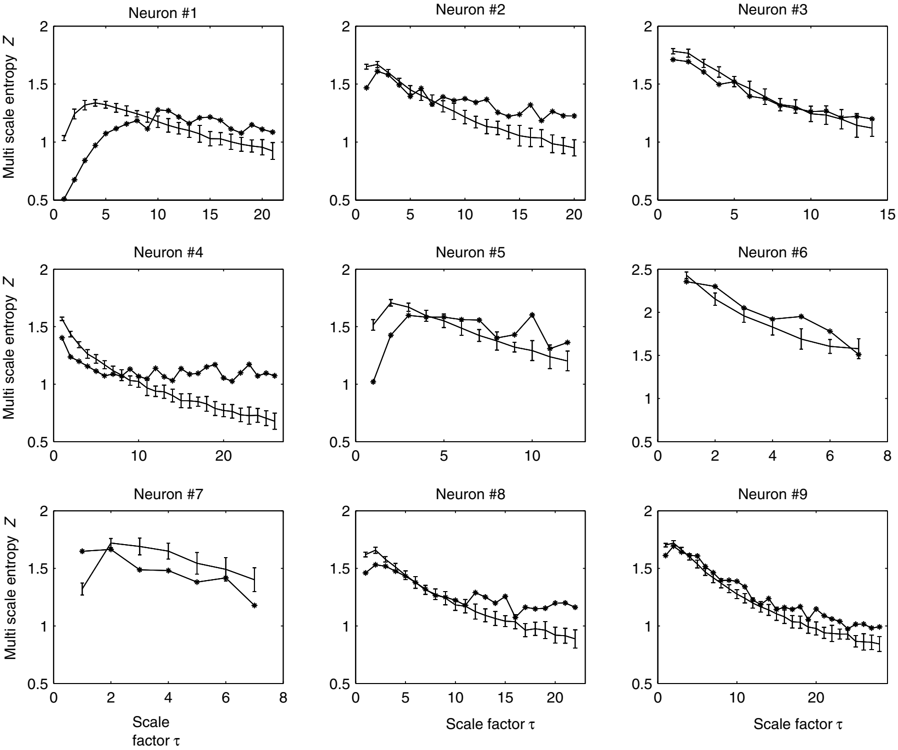

Figure 4: Multi-scale-entropy (MSE) analysis. Results are presented for each original ISIs ('*') and their surrogates. Error bars indicate the mean±std of Z values for the set of surrogates.

their surrogates showed primarily drooping entropy profiles against scale factor. Interestingly, some ISI sequences (Neurons #3,9) also showed gradually decreasing profiles but their entropy values at higher scale factor were still higher than that of the shuffled ISIs, thus rejecting the null hypothesis of renewal process.

Next the profiles of the running mean are shown (Fig. 5) for all ISI sequences along with their surrogates. Almost no neuron showed any sign of quick convergence to a steady average value but their surrogates, unequivocally, showed a fast convergence. Except neuron #6, a clear consistency was achieved among the first three methods of analysis.

We must point out an observation that the ISI sequences of neurons #6,7 were closest to the null hypothesis of renewal process and at the same time their firing rate was the lowest among all neurons. We firmly believe that these neurons also are fractal in nature but due to limited number of spikes in the considered ISI sequences (965 and 978 spikes, respectively), we could not conclusively prove the underlying long-range correlations.

Fig. 5 shows the results of spatio-temporal correlation analysis. Neurons which earlier rejected, with $Q > 1.96$, the null hypothesis of renewal process showed higher degree of correlated firing. Interestingly, there is a close match between the values of Q

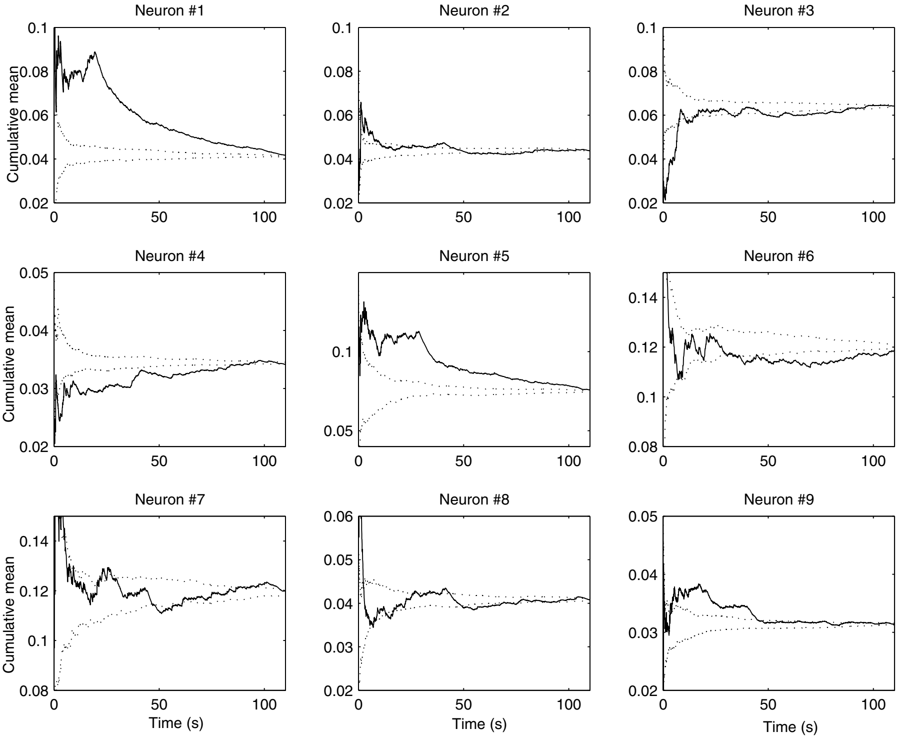

Figure 5: Cumulative moment analysis. The profiles of running or cumulative mean for ISIs (solid). The confidence levels (dotted) were estimated on the basis of shuffled sequences. Note the slow convergence of mean values for original sequences. Initial fluctuations and final matches are mainly due to boundary effects and should be ignored.

and the strength of correlated firing, possibly a signature of the formation of tightly coupled neuronal network composed of fractal neurons.

4 Discussion

Long-range power-law correlations has been observed in diverse kind of complex systems (See [16,17] for review) including brain. Here, we briefly mention the studies of long-range correlation phenomenon in the human brain spanning from extreme global, behavioral performances, to the extreme local, firing of a single neuron.

In the behavioral domain, memory effects, in the formation of long-range correlation, are reported in a human sensorimotor coordination experiment [18] in which a subject synchronizes his finger tapping with an external periodic stimulus. While investigating the patterns of eye movements in a visual search experiment, significant scaling properties emerge in difference across eye positions and their relative dispersion [19]. Such memory across eye movements may facilitate our ability to select our ability to emphasize certain useful information from the noisy environment [19].

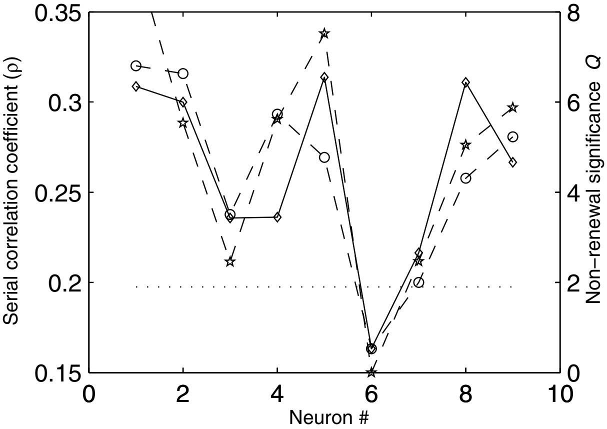

Figure 6: Spatial and temporal correlations. Spatial correlations are represented by the mean correlation coefficient between ISIs, and temporal correlations are represented by Q values as obtained by DFA (circle) and by MSE (asterisk). The horizontal dotted line represents the significance threshold and any entry above this line necessarily implies significant correlated structure in the associated ISI sequence. Note the tight relationship between these three profiles.

It is recently demonstrated [20] that envelope of the amplitude fluctuations of 10 and 20 Hz oscillations recorded from the scalp of human brain are correlated over thousands of cycles and these fluctuations obey power-law scaling behavior; scaling exponents are found to be subject-invariant. The power-law behavior of the global cortical oscillations is undisturbed by the presentation of sensory stimulus but the scaling exponents are decreased [11]. In addition, it is found that scaling exponents are consistent and reproducible for subjects over a span of days [21]. The temporal variability of human brain activity as measured by functional-MRI also shows power-law scaling behavior, which is, further, related with underlying neural activity [22]. Mentally active zones with larger haemodynamic responses, an indicator of activations, are described by highly temporally correlated processes, whereas mentally inactive zones are described by a random walk process. The degrees of long-range correlations in the global oscillations are found to be affected by the alertness [21], sensory perturbations [11], sleep stages [23].

Power-law scaling phenomenon is also observed in the spontaneous activities of intracortical field potential recordings from epileptic subjects [24]. Moreover, the degree of temporal correlations differ between epileptogenic and non-epileptogonic hippocampus [25].

However, in neurophysiology, it is the spontaneous firing pattern of neuron which was first investigated for the presence of spatio-temporal correlation [26-28]. By using methods derived from fractal time series analysis, long-range correlations have been shown in the rate of neurotransmitter secretion at *Xenopus* neuromuscular junctions [29], in medullary sympathetic neurons in cats [5,7,30], in auditory neurons [6] or in visual neurons [4] in cats (See [31] for review), in red nucleus of rostral midbrain in rats [32], in cultured neuronal networks [33] etc.

This paper shows for the first time that in vivo neurons of human hippocampus presented spike patterns which were correlated over long time scales. The presence of such long-range temporal correlations has been verified by the simultaneous application of different methods. It as also shown that the power-law scaling behavior was not due to the inter event interval distribution function. Further, it was shown that temporal correlations have been transformed into spatial correlations which may provide the substrate for information storage.

All these findings clearly point out that the power-law long-range correlation is an inherent characteristic of the neuronal dynamics present across many spatial and temporal scales. Immediately, two important questions arise: (i) What are the advantages of the long-range temporal correlations? (ii) What are the neural mechanisms based on which the long-range correlation emerges? Unfortunately, there has been no clear information available on the benefits of long-range correlation in the neuronal firing sequences. It has been proposed that many natural images are fractal [4], thus the underlying fractal dynamics might help in improving matched-filter performance of neuronal networks. Presence of temporal correlation can also facilitate the detection of weak sensory signals in noisy and changing environments [8,34,35]. Recently, it was shown [36] that activity of basal ganglia neurons in rats present long-range fractal dynamics, whose disruption would be related to the basal ganglia pathologies like Parkinsonian disease, which might support the relationship between fractality and the formation of active neuronal networks [37]. There has also been no consensus on the neurophysiological mechanisms which cause the fractal or long-range correlated firing pattern. Several candidate models, such as self organized criticality [38], fractal-rate point process [39,40], correlated noise driven integrate-and-fire model with time varying threshold [41] etc. have been proposed to reproduce the long memory in the spiking sequences. However more studies are needed to establish a direct relationship between the neuronal coding and the fractal firing pattern.

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