Fractal doubly stochastic behavior of neural spike trains recorded from rat *suprachiasmatic nucleus* neurons in vitro

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Abstract

The neurons of the suprachiasmatic nucleus (SCN) autonomously generate highly irregular patterns of spikes. We have shown that most SCN neurons exhibit truly stochastic interspike interval (ISI) patterns, while only 10% neurons are deterministic [1]. To understand the stochastic nature of the firing patterns, we investigate the ISI sequences of 150 SCN neurons recorded in hypothalamic slices. Fractal analyses using the periodogram, and Fano factor consistently reveal a 1/f-type power-law (fractal) behavior of the ISI sequences. We find that a gamma point process whose mean firing rate is modulated by a fractal binomial noise best describes the observed complex spiking activity of SCN neurons.

Keywords: suprachiasmatic nucleus, interspike intervals, fractal, long-term correlation.

1. Introduction

The SCN, the circadian pacemaker in mammals, is composed of thousands of neurons that produce spiking patterns with a sinusoidal modulation of their mean firing rates. However, ISIs of SCN neurons are quite irregular and complex. We have performed nonlinear analysis on ISI sequences recorded from SCN slices and found that about 90% of the SCN cell population generates truly stochastic patterns of spikes, while the remainders exhibit nonlinear determinism [1]. This finding in turn motivated us to investigate the very nature of the stochastic process underlying the irregular spiking activity of SCN neurons.

Neural spike trains, in general, have often been viewed as a stochastic signal of some renewal processes showing absolutely no correlation among their ISIs [7]. In several different occasions, such a description has been quite good enough [2,5]. However, as we will show in detail, the spiking activity of SCN neurons does not follow a simple renewal process but a more complex, yet, well-defined stochastic process known as a fractal point process. The hallmark of the fractal point process is the presence of long-term correlations within the sequence of ISIs. The spike train generated by the fractal point process exhibits a self-similar or scale-free behavior – i.e. no characteristic time scales dominate the dynamics of the underlying spiking process. The scale-free behavior indicates that long lasting correlations are present in the signal, extending over the entire range of time scales (thus, long-term correlation).

2. Methods

Male Sprague-Dawley rats (n=52; 40-100g) were housed in a temperature-controlled room (22-24⑤C) under a 12/12-hr light/dark cycle (light on 07:00-19:00) for at least 2 weeks prior to use. The rats were anesthetized with Nembutal (6 mg/100 g body weight) in the daytime of subjects, and then the brains were quickly removed and submerged in ice-cold artificial cerebrospinal fluid. Using a vibrating tissue slicer (Vibratome 1000, Technical Products International, USA), a block of hypothalamic tissue was cut into slices coronally at the thickness of 120-150 μm. The experimental procedures described above were in accordance with the guideline set by the Korea University College of Medicine Animal Research Policies Committee.

After 1-hr incubation in the recording chamber, extracellular recordings were commenced at room temperature (25-27⑤C). The recording electrodes made of borosilicate tubings (Sutter Inst. Co. USA) had a tip diameter of 2-4 μm with a resistance of 3-5 Mohm. Cell-attached patch (CAP) configuration without membrane rupture was achieved for extracellular, single-unit recording. In a CAP mode, a single action potential caused a transient capacitive current over the patch of membrane sucked into the pipette tip. This was recorded under voltage clamp conditions with a pipette potential of 0 mV. The recordings were performed using Axo-patch 200B amplifier (Axon Instruments, USA) in track mode from 173 SCN neurons for 20-40 minutes, and the ISI data were stored using pClamp software. The mean number of data points was 7,356 ± 2,961 (range: 1,422 - 19,213).

The *ISI histogram* was used to measure the relative frequency of occurrence $p_\tau(\tau)$ of an ISI τ. It is an estimate of the probability density function of ISI magnitudes. To examine the presence of long-term correlations in ISI patterns of SCN neurons, the periodogram and Fano factor were estimated. These statistical measures provide a way of investigating if a given data set has a self-similarity property. If their values estimated over brief periods of time are proportional to those estimated over longer periods, SCN neurons prove to exhibit a power-law (scale-free) behavior within ISI patterns, which is the hallmark of a fractal behavior. The periodogram (PG) estimates power spectral density (PSD) of the ISI sequences. For fractal signals, the PG exhibits a power-law behavior that varies with the frequency as $S(f) \propto f^{\alpha_p}$, particularly in the low frequency range. The Fano factor (FF) is the ratio of the variance of the number of spiking events in a counting number to the mean. The FF of a fractal stochastic process takes the power-law form T^{α_F} ($0 < \alpha_F < 1$) for large T, while it tends to stay in a constant value independent of T for a renewal process. The α_F is considered as the fractal exponent (scaling exponent) of the point process. The surrogate data test was used to confirm the presence of power-law characteristics in the ISI sequences of SCN neurons.

3. Results

ISI sequences from 150 SCN neurons recorded in 46 SCN slices were analyzed. Most neurons had ISIs with a unimodal distribution with an interval of 0.05 to 0.9 sec. The long tail was present in the long ISI range of the histogram (Fig. 1(a)). The most suitable stochastic model for describing the ISI histograms of the SCN neurons was investigated. The homogeneous Poisson process (HPP), fixed-dead-time-modified Poisson point process (DTMP), and the gamma renewal process (GRP) were tested as a candidate. It was found that the histograms were best fitted by the GRP (Fig. 1 (a)).

For the estimation of the PG, the data set was divided into T=500 sec. Each of these segments was subdivided into M=8,192 (2^{13}) bins, and within each bin the number of spikes was counted. The PG of the original data recorded from a typical SCN neuron and that of its surrogate data are presented in Fig. 1 (b) on a log-log scale. The PG of the original data exhibited a 1/f-type power-law behavior, in particular at low-frequency region (i.e. long-time range), whereas the PG of the surrogate data showed the flat white-noise like behavior in the same range. The average slope - i.e. the fractal exponent α_P - of the ISI data for the 150 neurons, estimated by regression analysis, was found to be 0.85±0.35, while that of the surrogate data was 0.03±0.20.

As another measure, the FF of the ISI data was estimated for the neurons and their surrogate data. The T was increased from 0.1sec with a step of 0.1sec. Figure 1(c) shows the FFs of the ISI data for an SCN neuron diverged in the power-law form, indicating the presence of long-term correlations among ISIs, whereas the surrogate data did not show the power-law behavior. The mean fractal exponent obtained from the FF curves of the 150 SCN neurons was $\alpha_F = 0.68 \pm 0.20$, which was significantly different from that of surrogate data ($\alpha_F = 0.03 \pm 0.15$).

A computational simulation of the ISI sequences of SCN neurons was performed to faithfully reproduce the observed stochastic dynamics underlying the ISI patterns. The model should generate neural spike trains exhibiting the ISI histogram and long-term correlations among ISIs similar to those obtained from the experiments. Because the ISI histograms of the SCN neurons were well fitted by the GRP, an ISI sequence was generated from the GRP whose firing rate was modulated by fractal stochastic noise to impose long-term correlations among ISIs, so called a fractal-binomial-noise-driven doubly stochastic gamma (FBNDG) point process. Figure 2 (a) shows a good agreement between the probability density function of the simulated data and the ISI histogram of the real ISI data from a typical SCN neuron. The simulated data provide a good fit to the ISI histogram of SCN neurons particularly in the long ISI region, whereas the simple GRP could not describe the long-tail of the histogram. Since the fundamental difference of the FBNDG from the simple GRP is the presence of long-term correlations among ISIs, the long-tail part of the ISI histogram is very likely associated with the long-term correlations. The PG and FF values were well fitted by the FBNDG model (Fig. 2 (b) and (c)).

4. Discussion

Long-term correlations and fractal behavior have been observed in patterns of action potential firings recorded in a variety of neuronal preparations [3, 4, 6, 8]. The presence of the fractal behavior throughout various brain regions suggests that the fractal behavior found in SCN neurons is a general feature of neurons, rather than a specific one pertaining to the SCN. Yet, the fractal property in SCN neurons is potentially important, because SCN neurons exhibit the cell-autonomous circadian rhythm in the mean firing rate. Thus, fractal behavior (or long-term correlations among ISIs) might be needed to make individual SCN neurons fire in a circadian fashion (The stochastic renewal processes alone are definitely not capable of producing the circadian modulation). In the present study, however, the recording time was not long enough to confirm any possible relationship between the fractal behavior and circadian oscillation in firing rates. In the future, long-term recordings from SCN neurons grown on an electrode plate will allow us to examine such a relationship.

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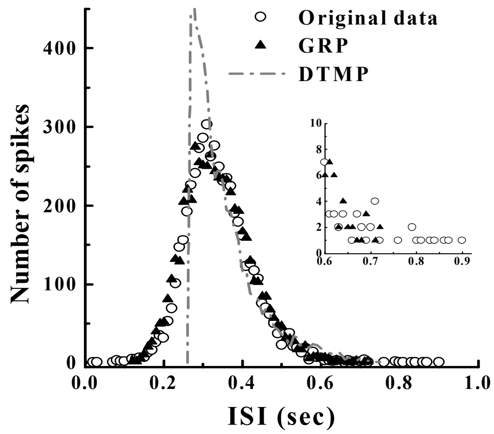
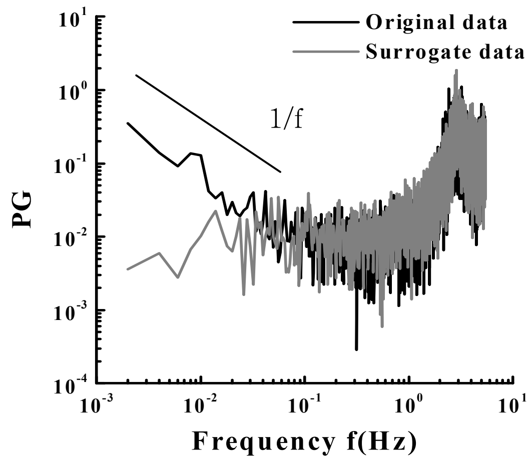
FIGURE LEGENDS

Fig.1. (a) ISI histograms for the original data recorded from a typical SCN neuron (o) and for the simulated data generated from the GRP (▲) and DTMP (-·-·-). The inset illustrates the failure of GRP to simulate the longer part of ISIs beyond the marker (↓). (b) The PG and (c) FF values of the original data recorded from a typical SCN neuron shows a 1/f-type power-law behavior. For each measure, the power-law behavior is removed in the randomly shuffled surrogate data.

Fig. 2. (a) Comparison of ISI histograms for the original ISI data recorded from a typical SCN neuron (o) and their simulated data (▲). The agreement between two histograms is well particularly in the long tail part, as depicted in the inset. Comparison of (b) the PG and (c) FF values for the original data recorded from an SCN neuron with the corresponding simulated data generated from the FBNDG.



(a)



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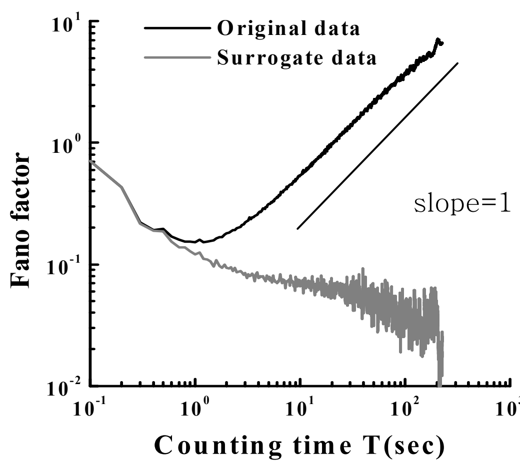

(c)

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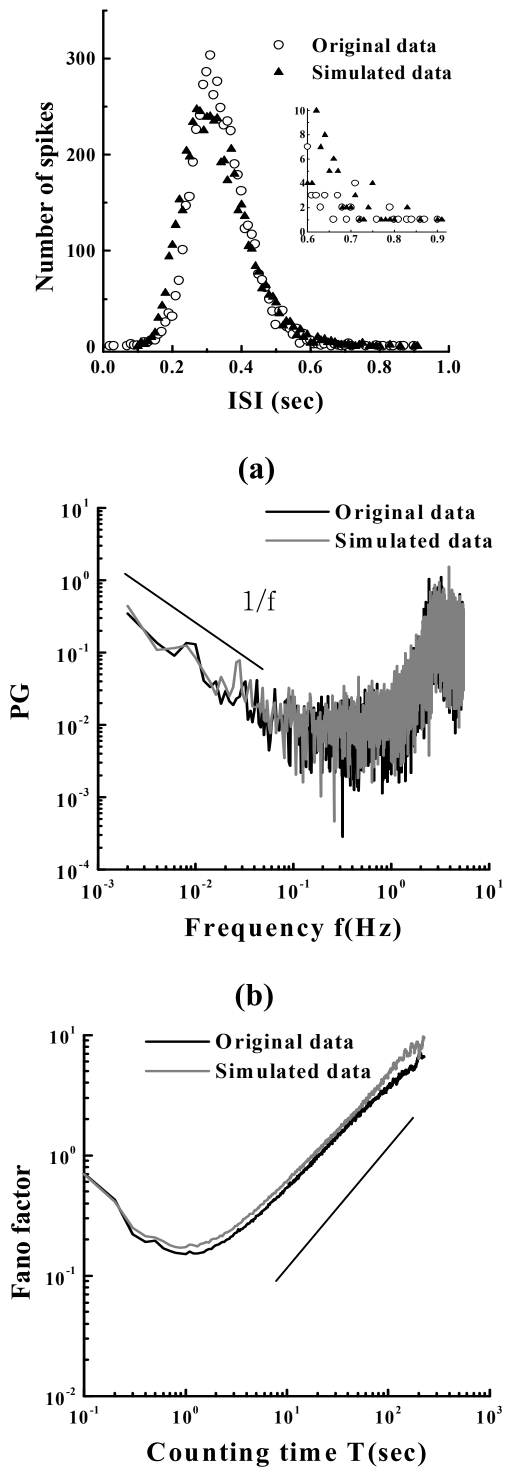

(c)

Fig. 2 Kim et al.

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