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Serial interval statistics of spontaneous activity in cortical neurons *in vivo* and *in vitro*

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Abstract

Stationary spiking of single neurons is often modelled by a renewal point process. Here, we tested the underlying model assumption that the inter-spike intervals are mutually independent by analyzing stationary spike train recordings from individual rat neocortical neurons *in vivo* and *in vitro*. All neurons exhibited moderate (*in vivo*) or weak (*in vitro*) negative first order serial correlation of neighboring intervals which was found to be significant in most cases. No significant higher order serial correlations were detected. The observed negative correlation lead to a strong reduction of the spike count variability by about 30% *in vivo*.

Keywords: Fano factor; Markov order; Renewal process; Serial interval correlation

1. Introduction

Stochastic point processes are frequently used as models for neuronal spiking. Renewal processes are a simple and well-studied class of point processes where intervals between successive events are independently and identically distributed (i.i.d.) according to a fixed interval distribution [10]. Renewal models may be defined in abstract mathematical form by specifying an arbitrary interval distribution which essentially characterizes the process. Equally, the output spike train of the biophysically motivated integrate-and-fire neuron driven by stationary Poissonian inputs is a realization of a renewal process [25,14,5]. The fixed interval distribution implies a constant rate of spike occurrence. The rate-modulated renewal process generalizes this concept to incorporate time-varying firing rate. The attractiveness and wide use of the mathematical renewal model is due to its simplicity which allows for analytic treatment and the calculation of accurate experimental predictions for statistical measures of interval and count statistics. At the same time, renewal models are suited for efficient numeric simulation. In this paper, we asked whether the spiking process of neocortical neurons is compliant with the renewal assumption. While these assumptions may be generally questioned, testing for the independence of inter-spike intervals (ISIs) is usually impaired by modulations in spike rate that may strongly influence the serial interval statistics. We therefore analyzed cortical spike trains from stationary spontaneous activity conditions. Specifically, we tested the null hypothesis of the mutual independence of ISIs in two different experimental conditions. First, spontaneous activity was recorded intracellularly *in vivo* from neurons in the somatosensory cortex of anesthetized rats. Second, we performed a set of *in vitro* experiments in rat layer 5 pyramidal neurons with injection of noise current that

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mimicked synaptic input bombardment of defined stochastic nature. Preliminary results have been published in abstract form [21].

2. Methods

2.1. In vivo intracellular recordings

Intracellular recordings were made from neocortical cells in S1 of Long-Evans rats (8 weeks or older) using sharp electrodes (60−120 MΩ) (Fig. 1). The animals were initially anesthetized with urethane (1 g/kg) and supplementary doses of ketamine–xylazine (20 and 2 mg/kg i.p.). We carefully selected data from $N = 8$ cells which exhibited long periods of continuous depolarization and stationary spontaneous spiking devoid of the strong membrane potential fluctuations (up/down states) usually observed during urethane anesthesia [13]. Spike rate (avg. 10.4 ± 4.5 per second) was constant in six cells but showed moderate slow modulation in two cells (Neurons 1 and 7 in Fig. 4a). To correct this we estimated the rate function with low time resolution (≈ 4 s, [19]) and subsequently demodulated the spike train [23,20].

2.2. In vitro noise current injection

Acute slices (400 μm) were obtained from S1 of Long-Evans rats (P15-28). Somatic patch clamp recordings (2−6 MΩ) were made from $N = 8$ regular spiking layer 5 pyramidal neurons (for details see [3]). Current traces of 300 or 1200 s duration were synthesized as superposition of independent EPSCs and IPSCs (decaying exponentials, 30 pA, 3 ms and 6 ms). Input was purely excitatory (E) or balanced with inhibition (E/I, ratio 2:1). Excitatory time series were modelled by a Poisson process or a gamma process of order $\gamma = 0.25$ (temporally clustered but serially independent inputs). Inhibitory inputs were Poisson. Current amplitude (nominal +100 pA) was adjusted for individual cells to obtain spike rates of 5–10 (average 7.7 ± 2) per second. The first 50 s of recording were discarded from the analysis to avoid potential onset transients.

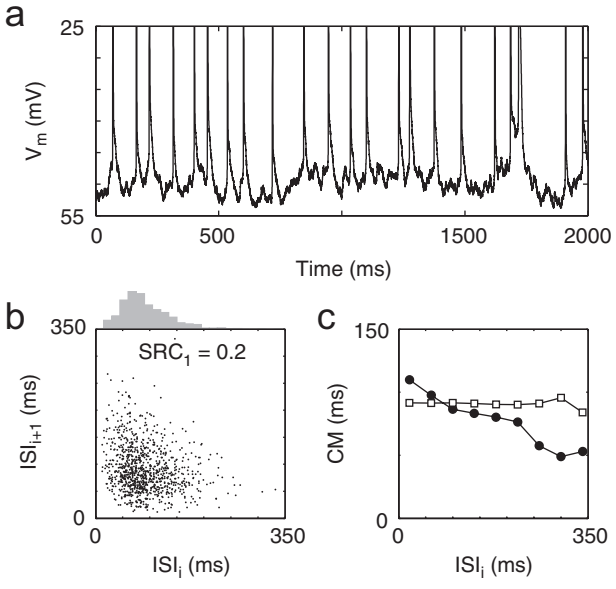

Fig. 1. (a) Intracellular voltage trace recorded *in vivo* covering 2 s of spontaneous activity. (b) The length of each interval is scattered against the length of the following interval to demonstrate their negative correlation. Gray histogram shows empirical ISI distribution. (c) Conditional mean (filled circles) in 40 ms steps and control (open squares) averaged across 100 random interval shufflings.

2.3. Spike train analysis

We quantified correlation of ISI pairs by the Spearman rank order correlation coefficient SRC_k of order k where each ISI is replaced by its rank among all intervals. The SRC_1 refers to the linear correlation between ranks of immediate neighbors, the kth-order SRC_k refers to the correlation of pairs ISI_i/ISI_{i-k} with $k-1$ intervals in-between. Significance of the SRC to be non-zero was established using the t-statistics. To compute the average SRC we used Fisher's z-transform. For the conditional mean CM ISIs were separated according to their length into classes of 40 ms width. For each class we then computed the mean of the following intervals [27].

Serial correlation is sensitive to rate non-stationarities [17,12]. Slow enough modulation evokes positive serial correlation of nearby ISIs. We tested individual *in vitro* experiments for non-stationary rate using the test suggested in [12]. Briefly, for the sequence of $n-1$ ISIs we calculated $n-m$ short term averages μ_i from consecutive samples of $m = 15$ ISIs and tested the null-hypothesis of normally distributed μ_i with parameters of mean $\langle ISI \rangle_n$ and standard deviation $\sigma(ISI)_n/\sqrt{m}$. We found a significant number of outliers ($P = 5\%$) in 16 of total 33 recordings.

To calculate the Fano factor (FF) we divided a given spike train into equal length counting intervals. Each interval contained on average 10 spikes to avoid significant bias effects due to short intervals [22,20].

3. Results

3.1. Serial interval correlation in vivo

In a first set of experiments, we measured spontaneous intracellular activity from cortical neurons in the somatosensory cortex of the anesthetized rat. A typical recording is presented in Fig. 1. The depolarized membrane potential and large voltage fluctuations reflected vivid synaptic input. We analyzed the spontaneous spike activity of each individual neuron for serial dependency of the ISIs. Fig. 1b shows the resulting ISI distribution (gray histogram) for a total of 989 spikes recorded during 90 s. From the scatter diagram where we plotted the duration of the ith interval against the duration of the $(i+1)$st interval it becomes evident that there is a tendency for long intervals to be followed by shorter ones and vice versa. This finds

expression in the significant ($P<10^{-3}$) negative first order serial correlation coefficient of $SRC_1 = -0.2$. The conditional mean in Fig. 1c (filled circles) measures the duration of the $(i+1)$st interval (ordinate) in dependence on the duration of the ith interval. The negative slope of this curve again clearly expresses the negative serial dependency of neighboring ISIs.

The negative first order serial interval correlation was found in seven of eight cells (Fig. 2a) which showed very similar strengths of correlation, with an average of -0.21. In one cell the SRC_1 was not significantly different from zero ($P>0.05$). None of the neurons, however, exhibited significant serial correlation of higher order and the average correlation was close to zero for all orders $k>1$ and in all neurons (Fig. 2b). Thus, non-zero serial correlation *in vivo* was restricted to immediately neighboring intervals.

3.2. Serial interval correlation in vitro

Somatic noise current injection *in vitro* enabled us to provide individual layer 5 pyramidal cells with synthetic input with predefined stochastic parameters. We modelled time series of excitatory and inhibitory input events as realisations of two independent renewal processes. Thus, individual synaptic input currents arrived with constant rate and without serial correlations. The noisy input resulted in a depolarized membrane potential, large voltage fluctuations and spike activity similar to what we observed *in vivo* (compare Fig. 1a and Fig. 3a).

We considered stable recordings only ($n=17$, see Methods) and calculated the SRC_k for all orders $k=1,2,\ldots,10$ for each individual spike train. The example of Fig. 3 exhibited a significant ($P<10^{-3}$) negative first order

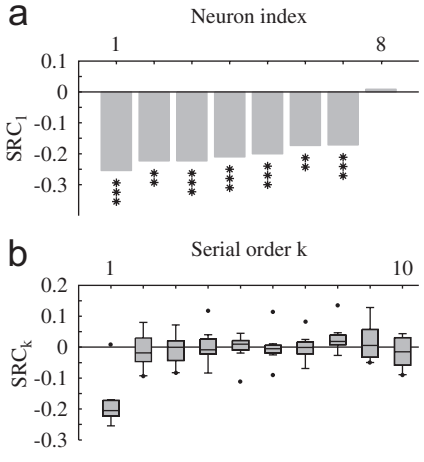

Fig. 2. Serial interval correlations *in vivo*. (a) First order serial correlation coefficient for eight individual neurons. Significance indicated by 2 ($P<0.01$) or 3 ($P<10^{-3}$) stars. (b) Distribution of correlation coefficients across all eight neurons for different serial order $k=1,2,\ldots,10$. Gray boxes delimitate the lower and upper quartile, black lines mark the median. Whiskers extend to 1.5 times inter-quartile range, black dots mark outliers.

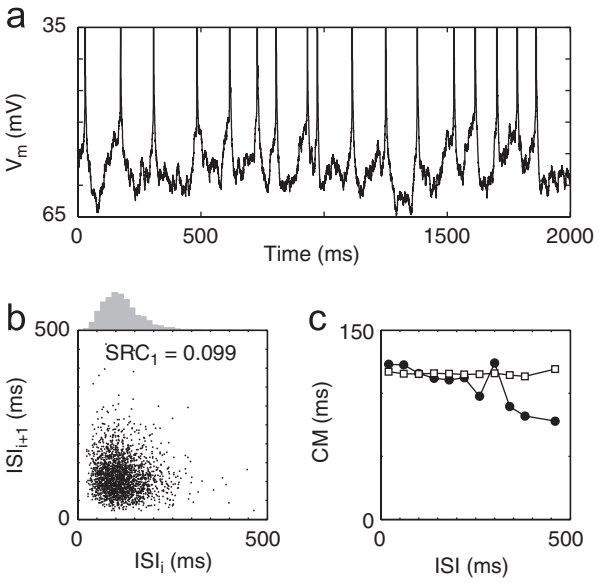

Fig. 3. (a) Membrane voltage *in vitro* in response to the injection of an excitatory shotnoise current. (b) Neighboring intervals are significantly correlated with $SRC_1 = -0.1$. (c) Conditional mean (filled circles) in 40 ms steps shows negative slope. Symbols as in Fig. 1.

serial correlation of $SRC_1 = -0.1$, while no significant correlation of order $k>1$ was detected. A negative SRC_1 was measured in all except one out of 17 experiments, and found to be significant in 13 cases ($P<0.05$) with an average correlation of -0.065. Grouping all experiments by the individual neuron, we find that all cells exhibited an average negative correlation of neighboring ISIs as shown in Fig. 4a. Higher order average correlation was close to zero (Fig. 4b) and individual values SRC_k for $k>1$ were significantly different from zero at the 5% significance level in about 3% and 9% of all cases for negative and positive correlation, respectively.

We recorded neurons in four different input conditions (see Methods). As shown in Fig. 4c, balancing excitation with inhibition (E/I) lead to a decreased average SRC_1 as compared to the case of pure excitation (E), irrespective of input clustering. Changing the excitatory input statistics from Poisson (gray bars) to a clustered process (white bars) slightly increased the average value of SRC_1.

3.3. Effect on second order count statistics

We investigated the effect of the observed negative serial correlation of ISIs on spike count variability, as measured by the Fano factor FF, in relation to the interval variability as measured by the squared coefficient of variation CV^2. For a given point process, count and interval variability are not independent. For a renewal process, and in the limit of long observation intervals, it holds that $FF = CV^2$ [10]. The more general analytic expression

$$\lim_{T\to\infty} FF = CV^2\left(1+2\sum_{i=1}^{\infty} SRC_i\right)$$

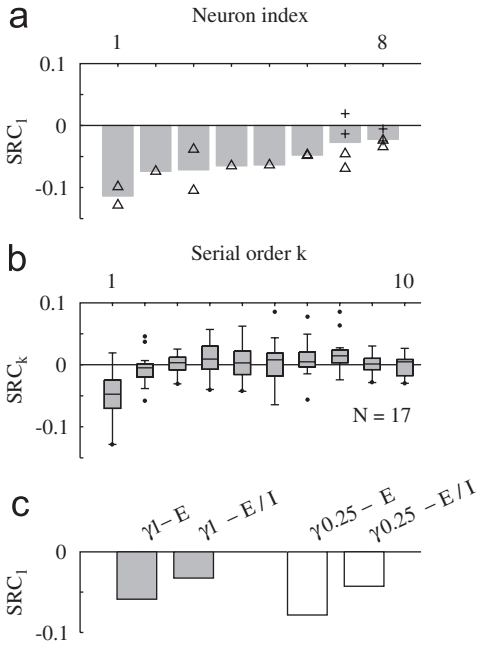

Fig. 4. Serial interval correlation *in vitro*. (a) Average first order correlation coefficient (gray bars) for individual neurons. Triangles mark significant ($P<0.05$) and crosses non-significant SRC_1 for individual experimental spike trains. (b) Distributions of serial correlation coefficients across $n=17$ individual experiments as pooled from all input conditions, for different serial order $k=1,2,\ldots,10$. (c) Average values of SRC_1 for individual input conditions as indicated.

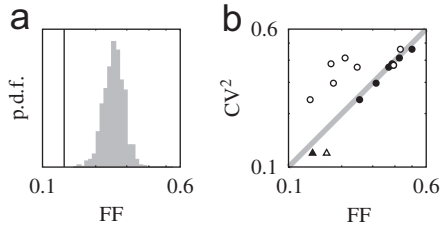

Fig. 5. Impact of serial interval correlation on spike count variability. (a) Distribution of *FF* from 1000 surrogate spike trains where intervals were randomly shuffled to destroy serial correlation and empiric estimate ($FF=0.13$, vertical line) for the same example neuron as in Fig. 1. (b) Empiric *FF* of spike count versus CV^2 of ISIs for individual neurons *in vivo*. Open symbols show empiric estimates; filled symbols show geometric mean across 1000 surrogates. Triangles refer to neuron 8 which did not exhibit significant ISI correlation.

accounts for serial correlation of order i [10,22,7]. In the case of our *in vivo* recordings we found significant first order ISI correlation in seven of eight neurons with an average correlation coefficient of $SRC_1=-0.21$ which implies that $FF<CV^2$. The predicted ratio of $FF/CV^2\approx 0.6$ is in good agreement with the average ratio of the empiric estimates where $FF/CV^2=0.68$ (cf. Fig. 5). As a control we generated surrogate renewal spike trains form the original spike trains by randomly shuffling all ISIs. This destroyed serial correlation and established renewal statistics where $FF\approx CV^2$ for all neurons as shown in Fig. 5b.

4. Discussion

Our results indicate that neocortical pyramidal neurons exhibit weak to moderate negative serial interval correlation of order 1, but no significant correlation of order 2 or higher. We conclude that the spiking process of cortical neurons violates the renewal assumption of independently distributed intervals. In agreement with the theoretical prediction, we could show that the observed serial correlation *in vivo* lead to a considerable reduction of the spike count variability in comparison to the renewal-based prediction. This has been previously demonstrated for electrosensory fibres in the weakly electric fish [22,7]. We can expect that both the strength and the order of serial interval correlation will depend on the actual firing rate. Here, we only analyzed stationary recordings with moderate rates of about 7–10 spikes per second. Future *in vitro* experiments will address the effect of different rate levels on serial interval correlation.

Up to now, there were surprisingly few attempts to investigate serial interval statistics in neocortical neurons. This may partly be due to the fact that a typical experimental setting implies a modulation of the firing rate which complicates serial analysis and which leads to long-ranged positive serial interval correlation [24,18,20]. In addition, extracellular recordings are subject to spike sorting errors which can be expected to have considerable impact on serial spike train statistics. Nakahama et al. [17] analyzed single unit activity in cat somatosensory cortex during a similar spontaneous state of 'quiet wakefulness'. They also report short-ranged serial dependency and estimated low Markov orders (typically 0 or 1) resulting in weak but strictly positive ($\approx +0.05$) first order serial correlation. Similar results were obtained by Baddeley et al. [1] in VI cells recorded in anesthetized cats and IT cells in the awake monkey. Negative first order serial interval correlation has previously been reported in other systems, in particular for neurons in the lateral superior olive (LSO) [27] and for electrosensory fibres in the weakly electric fish [22,7].

What could be the benefits of a negative serial interval correlation in terms of neural coding? The lower spike count variability effectively reduces the noise level of rate signals [22,7,4,11] and permits an increased information capacity for rate fluctuations on time scales that are longer than the mean ISI [6]. Recently, Lüdtke et al. [15] showed that short-term synaptic plasticity on time scales that match the mean ISI can retain serial correlation of afferent inputs and, in principle, could be exploited to further improve the detection of weak input signals on a noisy background.

What are the causes for the observed negative serial dependency in cortical neurons? The temporal structure of the afferent inputs provide a possible extrinsic source for serial output correlation. Slow modulations of the overall input, however, will cause positive correlation of the ISIs. Also, short and long ranged autocorrelation of colored

input noise exclusively produces positive correlation in the output of the I&F neuron [16,14]. We cannot rule out, however, that the detailed temporal structure of the network input *in vivo* significantly contributed to the result of a negative SRC_1 in our data. The major neuron-intrinsic factor are the afterhyperpolarization (AHP) currents responsible for spike-frequency adaptation (for references see [26,2]). Detailed biophysical models that incorporate physiologically motivated AHP currents have been shown to reproduce short-ranged negative serial interval correlation. In particular, the interplay of slow intracellular calcium dynamics and calcium-dependent potassium channels can mediate a cumulative AHP effect as has been demonstrated for compartmental models of cortical pyramidal cells by Wang [26] and for the LSO neuron by Zacksenhouse et al. [27].

The I&F model can be modified to incorporate a decaying threshold memory to reproduce negative serial correlation (e.g. [8,7,4,9,15]). Both types of models operate on physical time and thus serial correlation order will be dependent on the actual output rate of the neuron [2]. Simplified versions introduce a threshold memory of fixed length i that introduces serial correlation only up to order i, irrespective of the rate [6].

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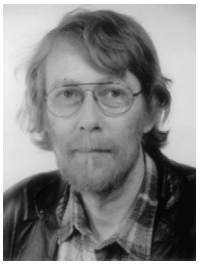
Victor Rodriguez-Molina was born in 1970 in Mexico, where he obtained his MSc in Biomedical Sciences (National Autonomous University of Mexico, UNAM, Mexico City) before he obtained his PhD in Biology in Germany from the Albert-Ludwigs-University in Freiburg. After association as a post-doc with the National Autonomous University of Mexico, UNAM, (Cuernavaca, Mexico), he is currently at the Autonomous University of Morelos State, UAEM, Mexico. His research interests are in the field of electrophysiological neuroscience, with a focus on physiological processes in cortical and hippocampal neural networks.



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