

A Rate-Independent Measure of Irregularity for Event Series and Its Application to Neural Spiking Activity

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Abstract—Although higher-order statistics of neuronal firing have been characterized in neuroscience, many analyses ignore the nonstationarity of the background firing rate. We discuss how to measure the irregularity of interspike intervals in a rate-independent manner. Under the framework of semiparametric statistical models, we develop an estimator of firing irregularity which remains after the effects of rate modulations are removed. We found that firing irregularity is robust and reproducible in neurons in olfactory cortex irrespective of the rate modulation during the task period. As the level of irregularity varies among neurons, we classified neurons in olfactory cortex by using the proposed measure as a feature.

I. INTRODUCTION

The discharge patterns in nervous systems can be highly irregular [1], [2], [3]. The irregular firing have been observed in cortical neurons of behaving monkeys [4], [5], [6], which triggered the debates for possible neural codes [7], [8], [9], [10] and utility of noise [11], [12]. Furthermore, because firing irregularity of individual neurons likely reflects, at least in part, both its intrinsic biophysical properties and statistics of input patterns, attempts have been made to use spike irregularity as a measure to classify neuron types [3], [13], [14].

In many studies [15], [16], [17], the irregularity of the firing pattern was characterized by the coefficient of variation of interspike intervals, C_V , which is defined as the standard deviation divided by the mean of interspike intervals [18], [19], [20]. C_V becomes 0 for completely regular spike trains and 1 for completely random spike trains generated by a (stationary) Poisson process. It was shown that it can be as large as 1 for *in vivo* neurons in the thalamus [21], [22], [23], [24] and cortex [25], [5], [6], indicating that their firings are highly irregular. The underlying mechanisms generating highly irregular spike trains were pursued by mathematical modeling of a single neuron [26], [27], [28], [29], [30] and a network [31], [32], [33], [34], [35].

However, C_V gives proper estimate only when the firing rate is constant [36], [37], [38]. In real situations where the firing rate changes over time, C_V is always biased or overestimated [39], [40], [41], [42] (Fig. 1 and the text for future explanations). Thus, the conventional measure C_V has a limitation in applying to a real neuronal data in which firing rates are expected to be modulated by various internal and external factors.

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We have previously proposed a new measure which is sensitive only to the irregularity of local interspike intervals, but not to the rate modulation [43], [44], [45]. The measure was derived based on the parameter estimation of a probabilistic model of spike generation, where the two factors, firing rates and irregularities, were orthogonalized [46]. This measure purely characterizes the irregularity of a single spike sequence which remains after the firing rate is detrended.

In this paper, we briefly review the derivation of the measure of spiking irregularity and show its application to the neural spiking activities recorded from rat olfactory cortex. First, we introduce a rate-modulated gamma process as a statistical model of spike generation and show how to estimate the parameter for spiking irregularity independently of the firing rate change. We show this estimator is robust against the firing rate change and, therefore, suitable as a measure of spiking irregularity. Next, we compute this measure for the spike trains recorded from olfactory cortical neurons. We found that the spiking irregularity is constant and not affected by tasks whereas the firing rate and the coefficient of variation C_V change largely during tasks. We classified the recorded neurons into three groups using the spiking irregularity in clustering analysis in addition to more commonly used parameters, the spike width and baseline firing rate. This application demonstrates the usefulness of the proposed measure taking advantage of its uniqueness.

II. SEMIPARAMETRIC MODELS AND PARAMETER ESTIMATION

A. Gamma distributions

Here we summarize the basic properties of the gamma distribution, which we will use as a part of our model.

We model firing of a neuron as a renewal process using a gamma distribution [47], which has been shown to fit the interspike interval distribution of neuronal activity fairly well [45], [48], [49], [50], [51], [52], [53], [54].

A probability density function q of interspike intervals of a spike train can be modeled using the following gamma distribution:

$$q(T; \xi, \kappa) = \frac{(\xi\kappa)^\kappa}{\Gamma(\kappa)} T^{\kappa-1} e^{-\xi\kappa T}, \quad (1)$$

where the random variable T denotes an interspike interval. The mean and variance of the interspike intervals are

$$\begin{aligned} \text{Ex}(T) &= \frac{1}{\xi} \quad \text{and} \\ \text{Var}(T) &= \frac{1}{\xi^2\kappa}. \end{aligned} \quad (2)$$

ξ is the mean firing rate and κ is called a shape parameter. When $\kappa = 1$, the distribution becomes the exponential distribution that is equivalent to the Poisson process where the spike train is completely irregular. When κ is large, a gamma distribution can be approximated by a normal distribution, whose variance decreases with increasing κ . In the limit of large κ , the interspike intervals become completely regular. Thus, κ is related to spiking irregularities. An important feature of the gamma distribution is that ξ always appears as ξT in $q(T; \xi, \kappa)$ and, therefore, changing ξ just stretches the distribution along T .

The parameters can be estimated by using the maximum likelihood method [55] as follows. Let $\{T^{(1)}, T^{(2)}, \dots, T^{(N)}\}$ be N observed interspike intervals. The likelihood that $T^{(l)}$'s are generated from the gamma distribution with $\{\xi, \kappa\}$ is given by

$$L = \prod_{l=1}^N q(T^{(l)}; \xi, \kappa). \quad (3)$$

In maximum likelihood estimation, the parameter values that maximize the likelihood are chosen. Without loss of generality, you can consider the maximization of the log-likelihood,

$$\log L = \sum_{l=1}^N \log q(T^{(l)}; \xi, \kappa). \quad (4)$$

The estimated parameters must satisfy

$$\frac{\partial}{\partial \xi} \log L = \sum_{l=1}^N \frac{\partial \log q(T^{(l)}; \xi, \kappa)}{\partial \xi} = 0 \quad \text{and} \quad (5)$$

$$\frac{\partial}{\partial \kappa} \log L = \sum_{l=1}^N \frac{\partial \log q(T^{(l)}; \xi, \kappa)}{\partial \kappa} = 0 \quad (6)$$

where

$$\frac{\partial \log q(T; \xi, \kappa)}{\partial \xi} \quad \text{and} \quad (7)$$

$$\frac{\partial \log q(T; \xi, \kappa)}{\partial \kappa} \quad (8)$$

are called score functions. Then, the parameters are estimated by solving the following equations,

$$\xi \bar{T} - 1 = 0 \quad \text{and} \quad (9)$$

$$\log(\hat{\kappa}) - \phi(\hat{\kappa}) - \log(\bar{T}) + \overline{\log T} = 0, \quad (10)$$

where the digamma function $\phi(\kappa)$ is defined using the gamma function $\Gamma(\kappa)$ as

$$\phi(\kappa) = \frac{\Gamma'(\kappa)}{\Gamma(\kappa)}. \quad (11)$$

Note that in the maximum likelihood estimation, the parameters are estimated by setting the sample averages of the score functions to be zero as in (5) and (6). This always works if the number of parameters is finite [55], [56].

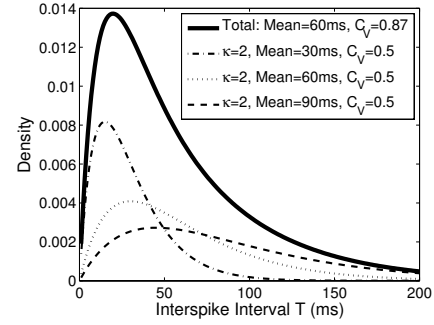


Fig. 1. An illustration of rate-modulated gamma processes. The mean interspike interval changes among 30ms, 60ms, and 90ms. C_V is 0.5 for each gamma distribution, whereas it is 0.87 for the total distribution which is obtained by equally mixing three gamma distributions. Note that the heights of the three gamma distributions are reduced to $1/3$.

B. The model

First, using an example, we illustrate how modulations in firing rates ξ result in overestimation of firing irregularity measured using C_V . Fig. 1 shows an example where κ is fixed to be 2 whereas the mean interspike interval increases from 30ms to 90ms. Let us assume that the first 10 interspike intervals have the mean value of 30ms, the second 10 have the mean of 60ms, and the last 10 have the mean of 90ms. Note that C_V for the total interspike interval distribution, which is represented by the thick line, is 0.87, which is surprisingly larger than the true value 0.5 for each gamma distribution. In this paper, we attempt to estimate κ which we assume to be constant regardless of the firing rate change, because the estimations of the firing rate profile and κ rather than C_V give the complete information of the spiking mechanism.

We assume that ξ for each interspike interval T is distributed according to a probability density $k(\xi)$, whose functional form is unknown. That is, the mean firing rate ξ at each time is generated randomly according to an unknown probability density $k(\xi)$. We consider the case where two observations of T are given for each ξ . That is, we assume that two consecutive interspike intervals in a spike train have the same firing rate. If there is only an interspike interval for a given ξ , it is impossible to estimate both ξ and κ from the single observation. Therefore two or more observations are required for each firing rate ξ . Here we minimally assume that two observations share a common firing rate ξ . Thus the rate correlation longer than two interspike intervals is regarded as the rate modulation whereas the difference between consecutive interspike intervals is regarded as irregularity.

Let $\{T_1, T_2\}$ be the two observations that are generated from the same firing rate ξ . The probability can be written as

$$p(\{T\}; \kappa, k(\xi)) = \int q(T_1; \xi, \kappa) q(T_2; \xi, \kappa) k(\xi) d\xi. \quad (12)$$

This distribution may look peculiar at first glance as it includes an integral. However, it can be understood as follows. The probability that an interspike interval coin-

cides with T under the firing rate ξ is the product of the probability that ξ is generated and the probabilities that T_1 and T_2 are generated with that ξ . The product becomes $q(T_1; \xi, \kappa)q(T_2; \xi, \kappa)k(\xi)$. Because the same T can be generated from a different ξ , ξ must be integrated to sum up all the probabilities. As this model is a mixture model weighted by $k(\xi)$, it can represent varieties of interspike interval distributions by changing the weight function. Note that this type of model is called a semiparametric model [56], [57], because it has both a scalar κ and a function $k(\xi)$ as parameters.

C. Estimation of spiking irregularity κ

Previously we showed that the maximum likelihood method works if the number of parameters is finite. However, a semiparametric model has infinite degrees of freedom because it has a function as an unknown parameter. Therefore, the maximum likelihood method does not work for our model [56], [43], [44].

Then, our strategy is that we estimate κ without estimating $k(\xi)$. It is known that only a part of parameters can be estimated optimally by modifying the score functions so that they are orthogonal to each other [57]. After the projection, the parameter can be estimated by setting the sample average of the modified score function to be zero as in the maximum likelihood estimation in (5) and (6).

For purposes of illustration, let us consider the fixed-rate gamma distribution defined in (1) as a simpler example. Here two score functions are already orthogonal to each other as the inner product of the two score functions are zero:

$$\int q(T; \xi, \kappa) \frac{\partial \log q(T; \xi, \kappa)}{\partial \xi} \frac{\partial \log q(T; \xi, \kappa)}{\partial \kappa} dT = 0, \quad (13)$$

where the inner product is defined in the function space with the probability distribution $q(T; \xi, \kappa)$ as a weight function. Fortunately, the estimating function in (9), which was derived from (5) by using the ξ -score function (7), does not depend on κ . Therefore, you can estimate ξ without estimating κ whatever the true parameters are, although you can also estimate κ with only a slight effort for this example having finite parameters. In general, the score functions can depend on all parameters and the combination of the equations such as (5) and (6) must be solved at once.

Here we only show the result. For our semiparametric model, the projected score function is obtained by subtracting the conditional expectation [43], [44], [58] as

$$\begin{aligned} & \frac{\partial \log p(T; \kappa, k(\xi))}{\partial \kappa} - E \left[\frac{\partial \log p(T; \kappa, k(\xi))}{\partial \kappa} \middle| T_1 + T_2 \right] \\ &= \log \left(\frac{T_1 T_2}{(T_1 + T_2)^2} \right) + 2\phi(2\kappa) - 2\phi(\kappa), \end{aligned} \quad (14)$$

where the digamma function $\phi(\kappa)$ is defined in (11).

κ can be estimated from N independent sets of observations, $\{T^{(l)}\} = \{T_1^{(l)}, T_2^{(l)}\}$, $l = 1, \dots, N$, as the value of κ that solves

$$\sum_{l=1}^N \log \left(\frac{T_1^{(l)} T_2^{(l)}}{(T_1^{(l)} + T_2^{(l)})^2} \right) + 2\phi(2\hat{\kappa}) - 2\phi(\hat{\kappa}) = 0. \quad (15)$$

Fortunately, this estimator does not depend on $k(\xi)$ at all. Thus you can estimate κ without estimating $k(\xi)$. In addition, this estimator is optimal because any estimator of κ has larger mean-square estimation error.

Although we skipped the detailed calculation in the derivation in (14), it is easy to show why it works. If there are many observations, the sample average in (15) approximates the expectation for the true distribution $p(T_1, T_2; \kappa, k(\xi))$. Because you can easily check

$$\int_0^\infty p(T_1, T_2) \left[\log \left(\frac{T_1 T_2}{(T_1 + T_2)^2} \right) + 2\phi(2\kappa) - 2\phi(\kappa) \right] dT = 0, \quad (16)$$

independently of $k(\xi)$, the estimated $\hat{\kappa}$ in (15) must be close to the true value κ .

The estimator works because the firing rate ξ only stretches the distribution ($T \rightarrow \xi T$) and it is cancelled out inside the logarithm. On the other hand, the coefficient of variation,

$$C_V \equiv \frac{\sqrt{(T - \bar{T})^2}}{\bar{T}}, \quad (17)$$

measures the variance around the global mean and cannot cancel out the local firing rate change.

D. Measure of spiking irregularity

We proposed a practical measure of spiking irregularity based on the estimator [44],

$$S_I \equiv -\frac{1}{N-1} \sum_{i=1}^{N-1} \frac{1}{2} \log \left(\frac{4T_i T_{i+1}}{(T_i + T_{i+1})^2} \right), \quad (18)$$

where T_i denotes the i th interspike interval and $\{T_1, T_2, \dots, T_N\}$ form a single spike train.

S_I becomes $1 - \log 2 = 0.307$ for a completely random spike train generated by a (stationary) Poisson process where $\kappa = 1$. It becomes zero for a completely regular or periodic spike train where $\kappa = \infty$.

If the value of κ is needed, it can be obtained by solving the following equation for $\hat{\kappa}$ numerically,

$$S_I + \log 2 - \phi(2\hat{\kappa}) + \phi(\hat{\kappa}) = 0. \quad (19)$$

Note that $\phi(2\kappa) - \phi(\kappa)$ is monotonic and, therefore, the correspondence between $\hat{\kappa}$ and S_I is one-to-one. This estimator works fairly well if the firing rate changes continuously and slowly [44].

III. RECORDINGS OF NEURAL SPIKING ACTIVITY

Here we summarize the experimental methods.

Behavioral training and testing were conducted as described in [59], [60]. Rats were trained and tested on an odor-cued two alternative choice discrimination task. A rat initiates a trial by entering the central odor-sampling port, which triggers the delivery of one of two odors. Each odor signals that water is available in one of the two goal ports. The rat responds by moving to one of them. A water reward is delivered for correct choices, whereas error trials are not rewarded, and no other feedback is provided.

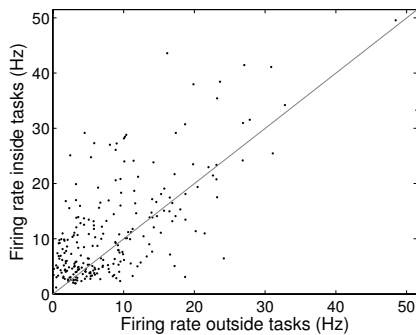


Fig. 2. Firing Rates outside and during task periods. The firing rate changes during task periods.

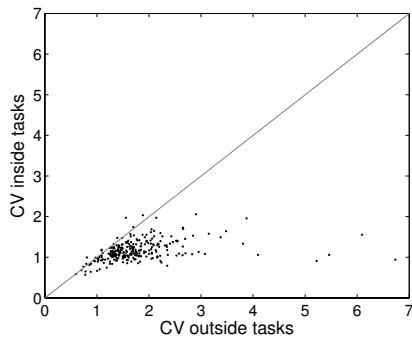


Fig. 3. Coefficient of variation C_V outside and during task periods. C_V tends to be large outside the task periods where the firing rates are not necessarily stationary. The correlation coefficient is 0.35.

Following training, rats were implanted with a custom-made chronic electrode drive consisting of six independently adjustable tetrodes in olfactory cortex (anterior piriform cortex, [61], [62]). Tetrode implantations and recordings were conducted as described in [63], [60]. Cells were isolated offline using manual clustering methods. Only units with good isolation and recording stability across the session were included in the analysis. All data analysis was performed using MATLAB (MathWorks, Natick, MA).

IV. RESULTS

Here we compare the stability of C_V and κ applied to real neuronal data. Firing rates, coefficients of variations C_V , Fano factors, and spiking irregularities κ were calculated for each neuron. The firing rates were calculated for two different periods: the period inside the tasks where the rats are in the presence of odor stimuli and the period outside the tasks. A firing rate was calculated for a neuron by averaging all trials. Each point in Fig. 2 corresponds to a neuron. The figure shows that the firing rate tended to be larger during the task. Next, the conventional measure of variability, the coefficient of variation C_V was calculated (Fig. 3). C_V 's (17) were calculated by collecting the interspike intervals inside or outside the task period across trials. The figure shows that C_V s outside the task periods are larger than those inside resulting in poor stability of this measure between inside and outside the task (correlation coefficient: 0.35).

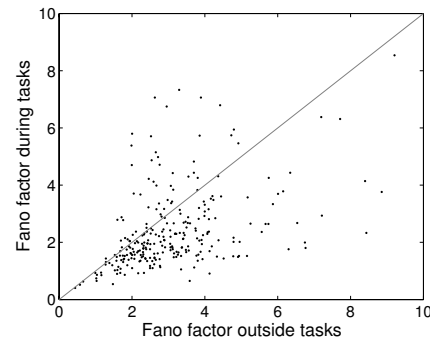


Fig. 4. Fano factor outside and during task periods. Fano factor is the variance over mean of the spike count. The window length for spike counts is 500ms. Fano factor tends to be large outside the task periods, which explain why C_V becomes large there.

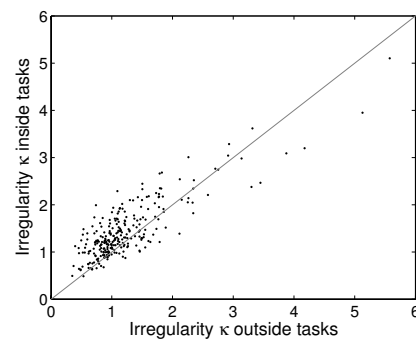


Fig. 5. Firing irregularity κ outside and during task periods. Each point corresponds to a single neuron. Irregularity κ is constant and is not affected by the task. The correlation coefficient is 0.85.

We hypothesized that poor correspondence of C_V between inside and outside the task is due to the higher variability in firing rates outside the task. To check the nonstationarity of the firing rate, we computed Fano factor which is defined as the variance over the mean of a spike count in some time window [18]. Fig. 4 plots Fano factors with 500ms windows outside and during the task periods. The numbers of spikes were counted for each separate 500ms window inside or outside the task period and their mean and variance for the whole recording including all trials were computed to obtain Fano Factors. The figure shows that Fano factors outside the task periods tend to be larger than those inside, accounting for why C_V is larger outside the task periods. Because κ is likely insensitive to firing rate modulations, we then tested whether κ stays constant between the two conditions. To calculate κ , S_I 's (18) were calculated from the spikes inside or outside the task period when the rats are presented odor stimuli and averaged over trials. From this averaged S_I , κ was obtained by solving (19). In fact, the large correlation coefficient (0.85) in Fig. 5 demonstrates that the spiking irregularity κ is highly reproducible and is not affected by the task. Although irregularity κ is constant over time for a given neuron, it varies largely by neuron, suggesting that it is useful for cell classification as we will show next.

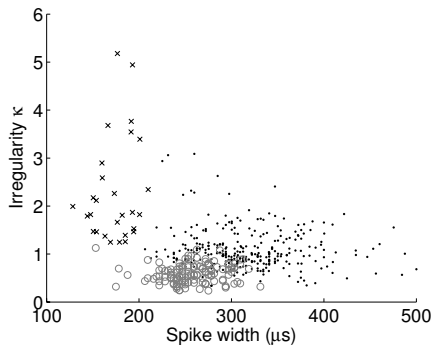


Fig. 6. Cell classification by clustering analysis according to spike widths, baseline rates and firing irregularities. The neurons are classified into three groups denoted by the circles, crosses, and dots. The neurons with small spike widths may be inhibitory interneurons.

Although extracellular recording features such as spike widths and firing rates have been widely used to classify neurons into two classes, wide- and narrow-spiking neurons, it is of great interest whether other parameters enable further classifications. Firing irregularity has been used to classify neurons both in slice experiments and *in vivo* extracellular recordings [14], [13]. Given the insensitivity of κ to firing rate modulations, κ may be suitable for this purpose. Hierarchical clustering was performed by using irregularity κ , spike widths, and baseline firing rates outside task periods of each neuron as features (Fig. 6). The neurons with narrow spikes are putative inhibitory interneurons [63]. Interestingly, the wide spiking neurons were further classified into distinct two classes. In the piriform cortex, it has been reported that there are at least two classes of pyramidal neurons that have different morphology and firing irregularity: one of them fires more regularly than the other [14]. Therefore, it is of particular interest to test whether these two classes within wide-spiking neurons actually corresponds to different class of neuron types in the future, using more definite methods such as genetically labeling neurons with molecular tags [64].

V. DISCUSSIONS

In this paper we demonstrated the constancy of the spiking irregularity. Recent studies showed that excitatory and inhibitory synaptic inputs are balanced in cerebral cortex [65] and spinal cord [66]. These results are consistent because it was shown that the spiking irregularity reflects the balance of synaptic inputs and, therefore, it is maintained at a constant level if the input balance is kept [45]. Thus, the spiking irregularity is also useful for studying the cortical circuits.

Some measures similar to S_I in (18) were used in previous studies to cancel out rate modulations [67], [68]. However, they are proposed ad hoc and do not have clear interpretations. In contrast, κ was derived based on the orthogonality in information geometry [46] and it has a corresponding parameter in the gamma distribution. Therefore, each value of κ specifies an interspike interval probability distribution, which can be utilized in information decoding [44], [69].

In the previous work, we demonstrated the information decoding or firing rate estimation can be improved by knowing irregularity levels [45]. This is possible because the irregularity shows how reliable the rate estimation is. For example, if you know that a neuron fires completely regularly or rhythmically, you can estimate the instantaneous firing rate only by taking an inverse of a single interspike interval. Similarly, it may also improve the spike sorting [70] by assigning the probability distribution of interspike intervals to each neuron.

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